ORIGINAL ARTICLE

Comparison of transdermal fentanyl with codeine/paracetamol, in combination with radiotherapy, for the management of metastatic bone pain

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ABSTRACT

Radiotherapy (R/T) is frequently used for palliative treatment of painful bone metastases; however, complete alleviation of pain is not always achieved. This study was designed to evaluate pain management outcomes and quality of life (QoL) measures in cancer patients with metastatic bone pain receiving a combination of R/T and either transdermal therapeutic fentanyl (TTS-F) patches or codeine/paracetamol.

A total of 460 palliative care patients with bone metastases who received R/T were enrolled in this prospective, open-label study. The patients were randomized to initially receive a total dose of 120 mg codeine/paracetamol per day or TTS-F patches releasing 25 μg fentanyl per hour. Pain measures were assessed on the basis of selected questions from the Greek-Brief Pain Inventory. Overall treatment satisfaction (scale, 1 to 4), QoL, and European Collaborative Oncology Group status were also recorded.

Among the 460 patients, 422 were eligible for evaluation. Pain measures in the TTS-F group demonstrated statistically significant improvements during the study that were superior to those in the codeine/paracetamol group ($p < 0.05$). Likewise, there was a significantly greater increase ($p < 0.05$) in the mean satisfaction score for patients in TTS-F group at every visit between baseline and month two. The vast majority (95.8 percent) of patients in the codeine/paracetamol group increased their medication dosage until the end of the study, whereas in the TTS-F group the respective percentage was only 6.1. Both treatments were generally well tolerated, with constipation as the most common side effect followed by sleep disturbances and nausea. The overall frequencies of side effects were higher in the codeine/paracetamol group.

The results therefore indicate that TTS-F offers more effective pain relief than codeine/paracetamol, in combination with R/T, in patients with metastatic bone pain, obtaining complete treatment satisfaction matched by improvements in their QoL.

Key words: bone metastases, pain, radiotherapy, fentanyl, codeine/paracetamol, palliation

INTRODUCTION

Moderate to severe pain is experienced by one-third of cancer patients receiving active therapy and by 60 to 90 percent of patients with advanced disease.[1,2] Bone pain is the most common type, and approximately 70 percent of patients with bone metastases experience pain at some point during the course of their disease. Advances in the diagnosis and treatment of cancer, coupled with advances in our understanding of anatomy, physiology, pharmacology, and pain perception, have led to improved care of the patient with metastatic bone pain.[3] Such patients are managed most effectively by a multidisciplinary approach with local radiotherapy (R/T) and the use of many analgesic agents, such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and biphosphonates, which provide additional benefit in the adjuvant setting. Moreover, the expertise of a wide range of healthcare professionals is of great significance in the management of pain attributable to bone metastases. Nevertheless, the ideal therapy for metastatic bone pain remains a subject of considerable debate among clinicians.

The transdermal therapeutic fentanyl system (TTS-F) (Duragesic, Janssen Pharmaceutical Products, LP, Titusville, NJ) has been used in the management of cancer

pain with promising results.[4,5] Open-label and prospective evaluations of efficacy, tolerability, and toxicity in cancer pain management have indicated that TTS-F is safe, with toxicities similar to those reported for other opioids. Constipation, nausea, and vomiting are the most common side effects.[6-11] Pain relief is rated as good by 49 to 82 percent of patients, and many as 63 percent of patients prefer TTS-F.[6,10] One large, randomized, open, two-period crossover study and a cross-sectional quality-of-life (QoL) study of TTS-F versus sustained-release oral morphine demonstrated more sustained pain relief and a lower frequency and severity of side effects, making TTS-F the preferred analgesic among participants.[12,13]

However, although the analgesic efficacy and tolerability of TTS-F has been established, until now there has been only one small study that demonstrated its efficacy and safety profile in combination with R/T in the management of metastatic bone pain.[14]

The present study was conducted to examine the efficacy and safety of TTS-F with that of codeine/paracetamol, in combination with R/T, in the palliative care setting in patients with metastatic bone pain. In addition, this study was designed to investigate pain management outcomes and QoL measures in these patients.

PATIENTS AND METHODS

From 1996 to 2003, a total of 460 palliative care patients with bone metastases experiencing moderate to severe chronic cancer pain were enrolled in this study. The local Ethics Committee approved the study, and each patient provided informed consent. The study was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983, and according to European guidelines for good clinical practice.

Eligible patients were aged at least 18 years, able to communicate effectively with study personnel regarding the nature of their pain and their QoL, and adequate communication and cooperation could be had from the patient's family. Inclusion criteria also included histologically confirmed malignancy with bone metastases, chronic moderate to severe cancer pain requiring strong opioid analgesics, and patient informed consent. Bone metastases were confirmed from computed tomography, magnetic resonance imaging, simple x-rays, or bone scintigraphy. Exclusion criteria included a history of opioid abuse, contraindications to opioids, and opioid use outside of the designated treatment regimen. Patients with the following conditions were excluded: cardiac, respiratory, or mental dysfunction; hepatic insufficiency (aspartate aminotransferase, alanine aminotransferase > 200 U per L); and renal failure (creatinine > 2.5 mg per dL).

All participants underwent palliative radiotherapy and then were randomized to initially receive the TTS-F 25 μg per hour patch applied every 72 hours or codeine/paracetamol at a total dose of 120 mg per day. No significant difference was detected between the two groups for pain measurements at baseline, confirming the homogeneity between the two groups. This was the reason that in both groups, approximately equianalgesic doses were given. Medication doses could be escalated during the trial for sufficient relief of emerging pain. All patients had already received palliative radiotherapy at the site of their painful bony metastases in 10 daily fractions (total dose of 30 Gy, 3 Gy per fraction, five days a week) with one or two radiation fields, by linear accelerator or 60Co. All patients that were included in the study had moderate to severe bone pain refractory to common analgesics and were naïve to mild or strong opioids. The type of this pain, called "nociceptive," is perceived with evidence of neuroradiologic tissue damage.

Data were collected on diary cards at the following time points of the study: baseline; 72 hours; seven, 14, and 28 days; and two months. Only patients with complete data for all relevant time points were included in the final analysis. Standard information collected on the patient's diary card at every visit included QoL, Greek-Brief Pain Inventory (G-BPI), overall treatment satisfaction, European Collaborative Oncology Group (ECOG) status, side effects, and use of concomitant medications. At baseline, both demographic and clinical characteristics were obtained, including family and educational status. A detailed medical history was also obtained and a complete physical examination was performed for each patient. Additional data included cancer location(s); type and etiology of pain; use of concomitant analgesic medications (NSAIDs or SAIDs); type, frequency, and grade of any side effects (i.e., constipation, nausea, sleep disturbances, vomiting, rashes/pruritus and sweating); ECOG status (0 to 4), and concurrent use of adjuvant hormonal therapy. Side effects were graded according to the Common Toxicity Criterion.[15]

For QoL assessment, a Visual Analog Scale (VAS) from 0 to 10 was used [highest (0) to worst (10)]. Three questions contained within the G-BPI (5, 9i, and 9ii) were used as an assessment of the patient's pain index.[16] These scores are shown in Figure 1. The Brief Pain Inventory (BPI) is a reliable yet simple pain assessment tool, which has been translated into Greek and validated.[16] Patients were also asked to rate their treatment satisfaction during the study by using a self-assessment scale (1 to 4), with 1 corresponding to "not at all satisfied," 2 to "fairly satisfied," 3 to "satisfied," and 4 to "completely satisfied."[17,18] The increment of the dose was dependent on the patient's needs. When the self-assessment scale was 1 or 2 and their pain score was ≥ 3, the drug dose was increased.

Changes in measurable scores between the TTS-F and codeine/paracetamol groups and their potent correlations were assessed using the chi-square test and analysis

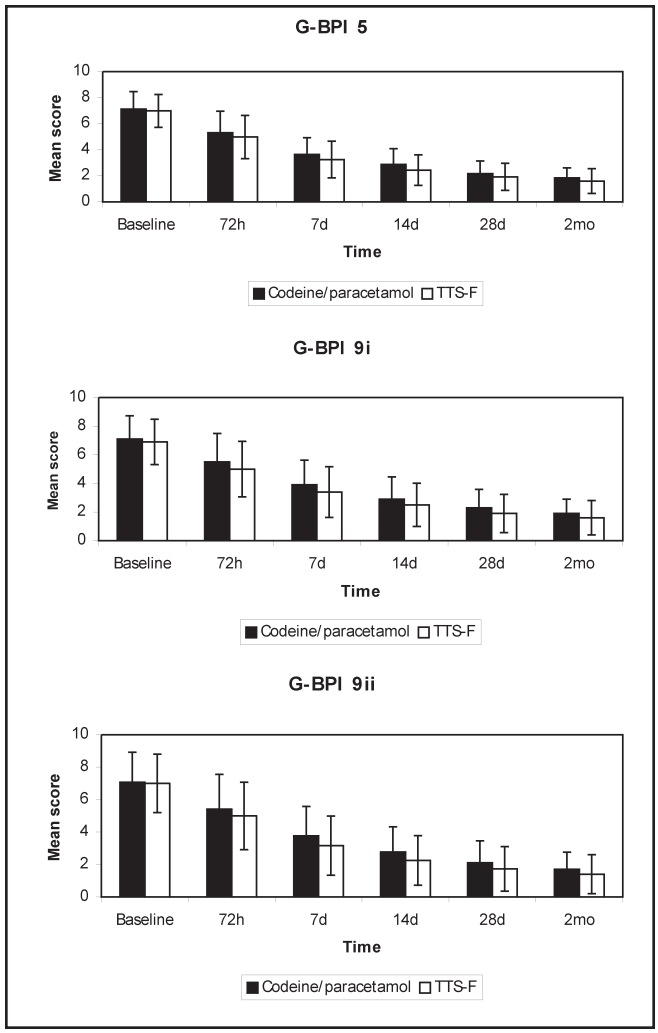

Figure 1. Pain measures: Results for questions GBPI-5, -9i, and -9ii for the two groups from baseline to month two.

of variance (ANOVA) for categorical and continuous variables, respectively. All tests were two-sided; $p < 0.05$ was considered statistically significant.

RESULTS

A total of 460 patients were enrolled in the study and were randomly assigned to the two treatment groups. Table 1 summarizes the patient population's general characteristics and demographics, primary and metastatic cancer site, and types of pain and adjuvant hormonal therapy. A total of 11 patients in the TTS-F group did not adhere to the protocol from baseline and five were excluded due to severe anemia, whereas in the codeine/paracetamol group nine and two patients, respectively, were also excluded for the same reasons. Ten patients in the TTS-F group did not receive palliative R/T, and three were excluded due to acute intestinal obstruction (ileus). These exclusions made 201 patients from the TTS-F group and 221 from the codeine/paracetamol group eligible for the study. During the course of the study, 17 (4.0 percent) patients withdrew. Nine (2.1 percent) withdrew as a result of uncontrolled pain relief, and one (0.24 percent) owing to side effects. The seven (1.7 percent) other patients died during the study.

Patients in TTS-F group started with an initial dose of 25 µg per hour; the codeine/paracetamol group with a total dose of 120 mg per day. In the TTS-F group the patients were allowed to take paracetamol/codeine with the onset of TTS-F application and, therefore, every six hours for the first 12 hours as rescue.

At the end of the study (month two), among the 215 patients in the codeine/paracetamol group who completed the study, only nine (4.2 percent) continued to receive the initial dose of 120 mg per day. Twenty (9.3 percent) patients increased their dose to 240 mg, 186 (86.5 percent) to 360 mg, and five (2.3 percent) withdrew because of uncontrollable pain, whereas in the TTS-F group, the vast majority of patients (184 out of 188; 97.9 percent) maintained their medication at the initial dose, and only four (6.1 percent) increased their dose to 50 µg per hour.

The summary statistics showed a progressive improvement in QoL, ECOG score, pain management, G-BPI (questions 5, 9i, and 9ii), and in overall treatment satisfaction for the two groups. Mean VAS QoL score 28 days post-baseline decreased gradually from 7.33 ± 1.09 to 4.43 ± 1.35 in the codeine/paracetamol group and from 7.28 ± 1.00 to 4.23 ± 1.31 in the TTS-F group. Likewise, ECOG score in the codeine/paracetamol group decreased from 2.33 ± 0.49 to 1.91 ± 0.59 and from 2.33 ± 0.63 to 1.98 ± 0.82 in the TTS-F group, showing a similar improvement between two groups. G-BPI scores (questions 5, 9i and 9ii) for the two groups are shown in Figure 1. All three G-BPI parameters decreased gradually during the study until month two in both groups, but patients in the TTS-F group experienced greater decrease, indicating greater pain relief, than patients in the codeine/paracetamol group ($p < 0.05$). For patients in the TTS-F group, the mean differences from baseline to study end (month two) in G-BPI questions 5, 9i, and 9ii were 5.39 ± 1.54, 5.38 ± 1.65, and 5.60 ± 1.87, respectively. For patients in the codeine/paracetamol group the mean differences were 5.26 ± 1.46, 5.22 ± 1.40, and 5.33 ± 1.63, respectively. Similarly, there was a significant greater increase ($p < 0.05$) in the mean satisfaction score for patients in the TTS-F group at every visit between baseline and month two (Figure 2).

Overall, both analgesic therapies were well tolerated. Table 2 indicates the percentage of side effects, expressed as the number per patient per visit. The most common side effect was constipation, with the highest incidence within patients in the codeine/paracetamol (28.5 percent) and TTS-F groups (18.4 percent) on the day seven visit. Respective highest rates for sleep disturbances were 20.4 percent in the codeine/paracetamol group and 18.4

Table 1. Patient characteristics and demographics			
Patients		**R/T + TTS - F**	**R/T + C/P**
Number		201	221
Gender	Male	95 (47.3)	124 (56.1)
	Female	106 (52.7)	97 (43.9)
Age (yr)		60.7 ± 13.2	60.9 ± 12.1
Age range (yr)		25 to 88	33 to 80
Family status	Married	139 (69.5)	158 (71.5)
	Single/divorced	61 (30.5)	63 (28.5)
Education	Primary	46 (23.0)	84 (38.0)
	Secondary	89 (44.5)	86 (38.9)
	University	65 (32.5)	51 (23.1)
Primary cancer location	Lung	58 (28.9)	86 (38.9)
	Kidney/bladder	61 (30.3)	54 (24.4)
	Gastrointestinal	33 (16.4)	31 (14.0)
	Breast	29 (14.4)	18 (8.1)
	Unknown	8 (4.0)	15 (6.8)
	Other	12 (5.9)	17 (7.7)
Site of bony metastasis	Thoracic spine	38 (18.9)	43 (19.4)
	Lumbar spine	47 (23.4)	52 (23.5)
	Cervical spine	36 (17.9)	39 (17.6)
	Thoracic + lumbar	24 (11.9)	31 (14.0)
	Pelvis	26 (12.9)	24 (10.9)
	Femur	9 (4.5)	10 (4.5)
	Scapula	21 (10.4)	22 (10.0)
Other metastases	Brain	29 (14.4)	38 (17.2)
	Gastrointestinal	23 (11.4)	9 (4.1)
	Lung	16 (8.0)	2 (0.9)
	Adrenal	12 (6.0)	7 (3.2)

Numbers in parentheses are percentages; C/P, codeine/paracetamol; R/T, radiotherapy; TTS-F, transdermal therapeutic fentanyl.

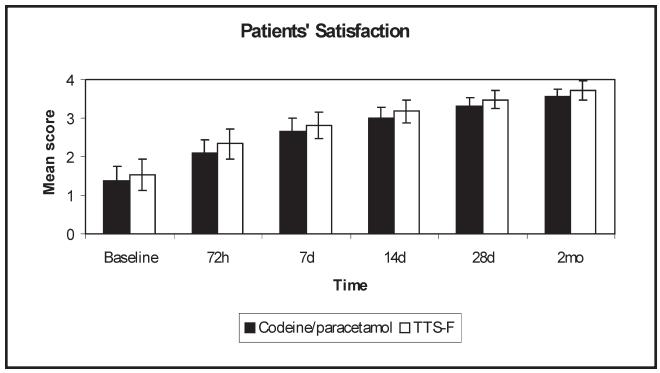

Figure 2. Mean patient satisfaction scores for the two groups from baseline to month two.

percent in the TTS-F group on the same visit. The highest incidences for nausea emerged only 72 hours post-baseline, and were 10.0 percent and 8.0 percent for the codeine/paracetamol and TTS-F groups, respectively. The overall frequencies of side effects showed a steady decline from an initial increase after the first doses of medications (baseline to 72 hours or day seven), and these side effects were successfully treated with appropriate medications (i.e., antiemetics, laxatives).

DISCUSSION

The vast majority of patients who die of cancer have tumor metastasis. Bone is the third most common organ involved by metastasis, behind lung and liver.[19] The increasing age and size of the population leads to an increased number of cases of cancer; this, coupled with longer patient survival, increases the incidence of metastatic lesions to bone. Patients with bone metastases most often present with pain as the principal symptom. As more patients are living with bone metastases, the main challenge for healthcare providers is to provide sufficient analgesia to improve patient QoL. Current management of painful bone metastases involves a multimodality approach, including systemic therapies—chemotherapy, hormone therapy, analgesics, and other medications (i.e., bisphosphonates)—and R/T.[20-22]

External-beam palliative R/T is an important technique for treatment of metastatic bone pain. Irradiation achieves at least partial relief of pain in 80 to 90 percent of patients, with better outcome in those with a limited number of well-localized bony metastases.[23-26] The optimal dose and fractionation regimen for palliative therapy of metastatic bone lesions has been debated.[24,26,27] It can be given as a single fraction or in multiple fractions over several days.[28]

Table 2. Side effects during study period

Time	Group	Constipation	Nausea	Sleep disturbances	Vomiting	Rash/pruritus	Sweating
Baseline	TTS-F	6 (3.0)	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
	C/P	15 (6.8)	5 (2.3)	6 (2.7)	3 (1.4)	0 (0.0)	0 (0.0)
72 hours	TTS-F	37 (18.4)	16 (8.0)	37 (18.4)	13 (6.5)	3 (1.5)	9 (4.5)
	C/P	66 (29.9)	22 (10.0)	40 (18.1)	3 (1.4)	0 (0.0)	2 (0.9)
7 days	TTS-F	37 (18.4)	20 (10.0)	37 (18.4)	11 (5.5)	3 (1.5)	9 (4.5)
	C/P	63 (28.5)	19 (8.6)	45 (20.4)	3 (1.4)	1 (1.5)	2 (0.9)
14 days	TTS-F	36 (17.9)	19 (9.5)	31 (15.4)	6 (3.0)	3 (1.5)	9 (4.5)
	C/P	54 (24.4)	16 (7.2)	37 (16.7)	1 (0.5)	2 (0.9)	1 (0.5)
28 days	TTS-F	29 (14.7)	11 (5.6)	17 (8.6)	2 (1.0)	1 (0.5)	2 (1.0)
	C/P	46 (21.0)	11 (5.0)	16 (7.3)	2 (0.9)	6 (2.7)	0 (0.0)
2 months	TTS-F	30 (16.0)	12 (6.4)	5 (2.7)	2 (1.1)	1 (0.5)	0 (0.0)
	C/P	43 (20.0)	6 (2.8)	5 (2.3)	1 (0.5)	2 (0.9)	0 (0.0)

Numbers in parentheses are percentages; C/P, codeine/paracetamol; TTS-F, transdermal therapeutic fentanyl.

Opioid analgesics remain the cornerstone of pharmacotherapy for pain, with morphine long being the gold standard for cancer-associated pain. Short-lived drugs are generally favored because they are easier to titrate than those with a long half-life. The optimal route of administration of opioids is oral; however, bowel obstruction, severe vomiting, or coma may preclude this route. The TTS-F system is a long-acting, controlled-released opioid preparation that limits the inconvenience of 24-hour administration of other drugs. Several studies have examined its effectiveness and safety as an analgesic,[4,5,10,29,30] for which it was recently added to the WHO Step III ladder for chronic and intractable pain.[11] More recently, attention has been drawn to the use of opioids for the treatment of carefully selected patients with chronic cancer pain, especially in the palliative care setting.[9,31]

In our study we have investigated the combined analgesic effectiveness and safety profile of the two treatments in cancer patients with strong intolerable or chronic pain. We demonstrated that in combination with R/T, TTS-F was superior to codeine/paracetamol in improving the three G-BPI parameters and the mean satisfaction score from baseline to study end. Both analgesic therapies improved VAS QoL and ECOG scores similarly and were generally well tolerated and safe with patients in the TTS-F group, which experienced marginally fewer side effects. It should be noted that for reasons of providing best analgesic treatment, dose escalation was permitted during the study period. The majority of patients (95.8 percent) in the codeine/paracetamol group increased their medication dosage from 120 mg to 240 mg and 360 mg per day, whereas only four patients (6.1 percent) in the TTS-F group increased their dosage from 25 μg per hour to 50.0 μg per hour for adequate pain alleviation. Considering this, the final differences in the improvement of G-BPI, QoL, ECOG, and satisfaction scores would have been greater between the two groups if we had maintained the initial doses throughout the study.

TTS-F has been available in Greece since 1996, from which point we have continued to monitor and study the safety profile and effectiveness in cancer patients admitted to the palliative care and pain relief clinic. We have previously investigated the possibility of direct conversion to TTS-F in a population of cancer patients (n = 130) previously receiving codeine/paracetamol for cancer pain relief and requiring strong opioids for adequate analgesia.[9] We demonstrated that with careful patient selection and under controlled conditions, TTS-F is a feasible option. More recently, interest has centered on a generally held perception that is possible to use TTS-F as a single opioid in cancer patients naïve to mild or strong opioids with intractable or chronic pain (pain index scores ≥ 6), that is, on Step I of the WHO ladder.[32,33] In a clinical trial conducted in our center, we examined 113 patients with high pain index scores and demonstrated the safety and efficacy of bypassing Step II for carefully selected populations.[9] In another recent study conducted in our center (n = 1,828), we showed that TTS-F offers a safe, well-tolerated pain relief treatment for carefully monitored patients with cancer pain experiencing difficulties in their pain management while progressing up the WHO ladder.[34]

The present study investigated the analgesic efficacy and the safety profile of TTS-F with those of codeine/paracetamol in combination with R/T for metastatic bone pain. The results support a previous small, multicenter, randomized study in which TTS-F was compared with oral codeine/paracetamol in combination with R/T,[14] but the present study enrolled a greater number of patients with bone metastases (n = 460 vs. n = 26), and escalation of medication doses was permitted during the study for optimal pain alleviation. Moreover, because this study was conducted in a single center in which there is an integrated and experienced pain relief and palliative care team, conformity in patient management was assured during the study period.

In conclusion, our study showed that TTS-F in combination with R/T offers a greater degree of pain relief for cancer patients with painful bone metastases than codeine/paracetamol with the use of a single 25 μg per 72 hours patch in the majority of patients. Patients with moderate to severe persistent intolerable or chronic pain who had not been previously prescribed with a strong opioid will obtain complete treatment satisfaction matched by improvements in their QoL without serious side effects as a result of the pain relief provided by TTS-F.

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