

ORIGINAL ARTICLE

Radiotherapy combined with daily escitalopram in patients with painful bone metastasis: clinical evaluation and quality of life measurements

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Summary

Purpose: To prospectively assess the efficacy of the selective serotonin inhibitor escitalopram on painful bone metastases, in combination with external beam irradiation.

Methods: Forty-three patients with cancer metastatic to bone and suffering from depression were treated with 3 Dimensional Conformal Radiotherapy (3DCRT) (30 Gy; 3 Gy/fraction, 5 days/week) combined with escitalopram (20 mg/day). Pain relief was evaluated with Wong-Baker Faces Pain Scale. The patients reported outcome using a RTOG-EORTC quality-of-life self-questionnaire (QLQ-C30 v3.0) and the status of depression according to

Hamilton Scale (HAM-17). The assessment was performed at baseline and 6-8 weeks after radiotherapy.

Results: Patients treated with radiotherapy and escitalopram tended to show a good response to pain and improvement of their quality of life.

Conclusions: Though our data concerned a rather small number of patients, addition of escitalopram to 3DCRT accomplished a high clinical benefit rate on neuropathic pain from bone metastasis.

Key words: bone metastasis, cancer, depression, escitalopram, quality of life, radiotherapy

Introduction

Bone is one of the most common sites of metastasis in patients with advanced cancer, and metastasis to bone results in significant skeletal morbidity [1]. The majority of bone metastases arise from tumors such as breast, prostate, thyroid, lung, and kidney [2]. Radiotherapy represents an effective treatment for preventing skeletal-related events in patients with bone metastases and may preserve functional independence and quality of life.

Neuropathic pain is a common symptom in bone metastasis. The management of this condi-

tion remains a difficult clinical task and standard treatment has yet to be established. Neuropathic pain may arise as a consequence of a lesion affecting the somato-sensory system [3]. It may be associated with abnormal sensations called dysesthesia, which occur spontaneously and allodynia that occurs in response to external stimuli. Neuropathic pain may have continuous and/or episodic components. It may be divided into peripheral, central, or mixed (peripheral and central) pain.

Recent trials indicated an effect of serotonin/nor-adrenaline reuptake inhibitors (SNRIs) on peripheral neuropathic pain [4-8]. Serotonin (5-HT) is involved in pain modulation via descending

pathways in the central nervous system. Escitalopram is a selective serotonin reuptake inhibitor (SSRI) [9]. It is the S-enantiomer of the selective serotonin inhibitor citalopram, which is a racemate of both R- and S-enantiomers. The S-enantiomer has been shown to be responsible for the pharmacological effect of citalopram [10]. A recent review suggested that R-citalopram via an allosteric mechanism might decrease the association of S-citalopram with the serotonin transporter and thereby reduce the effect of S-citalopram [11]. This would mean that escitalopram might be more efficient than the same amount of the S-enantiomer in the form of citalopram, a hypothesis supported by a clinical trial comparing the two drugs in depression [12].

In this manuscript, we present the results of a prospective study in bone metastatic depressed patients investigating the effect of escitalopram in relief pain and improvement of quality of life (QoL) in patients that underwent radiotherapy.

Methods

Inclusion and exclusion criteria

Forty-three patients suffering from depression were enrolled in our trial and included in the data analysis. Beyond the confirmation of depression, the inclusion criteria were pathologically confirmed carcinoma, radiologically confirmed bone metastasis, age between 18 and 80 years, Karnofsky Performance Status higher than 60 and adequate hepatic and renal functions. The exclusion criteria were hypersensitivity to escitalopram, simultaneous administration of MAO inhibitors, diagnosis of bipolar disorder, schizophrenia, drug addiction or dependence, organic brain syndrome and mental retardation, spinal cord compression, pregnancy and lactation; and patients with significant risk factors such as renal failure (creatinine clearance <30 ml/min), pharmacologically uncontrolled epilepsy, depression with suicidal attempts, diabetes mellitus, advanced age, liver cirrhosis, bleeding tendency, simultaneous administration of drugs lowering the threshold of convulsive readiness or causing hyponatremia. Patients consuming little ethanol were enrolled only after careful consideration and discussion with them. All participants were free of any psychoactive medications for at least 8 weeks before the administration of escitalopram.

Pretreatment evaluations

Pretreatment evaluations were performed within 2 weeks before the start of treatment and included history, physical examination, complete laboratory tests and CT or MRI of the painful metastatic region. All outpa-

tients were evaluated by the same psychiatrist using the relevant rating scale for depression (HAM-D 17) and general clinical condition at baseline and weekly thereafter for a period of 8 weeks.

Study objectives

The main endpoint of this study was pain relief as a result of escitalopram in combination with radiotherapy and was assessed with the Wong-Baker Rating Scale [13]. Two secondary endpoints were evaluated in our study: the QoL according to the RTOG-EORTC quality-of-life self-questionnaire (QLQ-C30 v 3.0 [14] and the status of depression according to Hamilton Scale [15-18]. Assessments were performed at baseline and 2 months after radiotherapy.

Treatment

The patients were scanned with 5 mm slice thickness in simulation CT scan and the CT datasets were transferred to Prosoma® System through DICOM III network. Depending on the localization of the metastatic bone lesion, different CTs were performed. The photon energy used was 6MV. If dosimetry was not optimal 15MV was also used. All patients underwent a radiotherapy schedule of 10 fractions of 3Gy, 5 days per week. Radiotherapy was given as a 3-D conformal technique by using the ECLIPSE VARIAN® treatment planning system.

Escitalopram was taken orally (20 mg/day, flat dose), in 43 patients with metastatic bone cancer. One patient was withdrawn due to an allergic reaction.

Escitalopram was continued after the end of radiotherapy. The study design is shown in Figure 1.

Evaluation of response

Six to eight weeks after the end of radiotherapy all patients were evaluated with physical examination and complete laboratory tests, as shown in Figure 1. Response to radiotherapy was assessed by CT or MRI. Response to combined irradiation and escitalopram was evaluated in terms of pain relief with Wong-Baker Faces Pain Scale and in terms of QoL by using the EORTC self-questionnaire (QLQ-C30 v 3.0). Depression

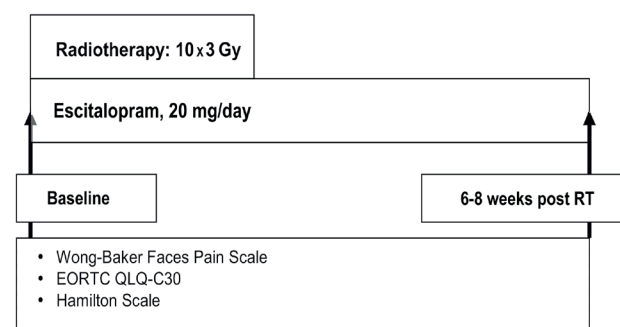


Figure 1. Study design.

Table 1. Hamilton Scale pre and post treatment

Item	Pre-treatment		Post-treatment		p-value
	Mean	±SD	Mean	±SD	
1	2.16	0.15	0.95	0.03	0.001
2	2.00	0.00	0.53	0.07	0.001
3	2.16	0.15	0.10	0.01	0.001
4	2.00	0.00	0.44	0.08	0.001
5	2.00	0.00	0.10	0.02	0.001
6	2.00	0.00	0.12	0.06	0.001
7	3.42	0.07	0.98	0.04	0.001
8	2.58	0.07	0.95	0.03	0.001
9	2.00	0.05	0.00	0.00	0.001
10	3.58	0.07	1.07	0.15	0.001
11	3.62	0.06	1.02	0.02	0.001
12	2.00	0.02	1.37	0.09	0.001
13	2.00	0.03	0.58	0.07	0.001
14	2.00	0.07	0.95	0.32	0.001
15	3.00	0.01	1.47	0.09	0.001
16	2.00	0.01	0.40	0.07	0.001
17	0.58	0.08	0.00	0.00	0.001

was evaluated with the Hamilton Scale.

Statistics

The statistical comparisons pre and post treatment were assessed by using the Wilcoxon non-parametric test. The test was used to analyze the differences of parameters at baseline and 6-8 weeks after radiotherapy. Values of $p < 0.05$ were considered to be statistically significant. The whole analysis was performed by using the SPSS version 15 (Chicago, IL).

Results

Treatment compliance

All patients completed their treatment with radiotherapy in combination with escitalopram. In one patient escitalopram was interrupted after an allergic reaction.

Response evaluation

A total of 43 patients with metastatic bone cancer (17 women, 26 men; mean age 58 years; range 36-80) were finally eligible for analysis. Analysis of the QoL using Wong-Baker and Hamilton Scale indicated a good response when radiotherapy was combined with escitalopram. Complete response to pain was observed in 4 out of 43 (9.3%) patients and partial response in the remaining 39 (90.7%) patients, while there was no patient with no clin-

Table 2. QLQ-C30 pre and post treatment

Item	Pre-treatment		Post-treatment		p-value
	Mean	±SD	Mean	±SD	
1	3.65	0.48	1.98	0.60	0.001
2	3.47	0.50	2.00	0.58	0.001
3	3.47	0.55	1.93	0.67	0.001
4	3.49	0.51	1.84	0.61	0.001
5	3.65	0.48	2.02	0.67	0.001
6	3.67	0.47	2.00	0.69	0.001
7	3.44	0.50	1.95	0.72	0.001
8	3.44	0.50	1.91	0.68	0.001
9	3.35	0.48	1.91	0.68	0.001
10	3.44	0.50	1.95	0.65	0.001
11	3.35	0.61	1.95	0.53	0.001
12	3.42	0.50	1.98	0.56	0.001
13	3.35	0.65	1.95	0.62	0.001
14	3.12	0.85	2.95	0.90	0.038
15	3.14	0.83	3.02	0.91	0.087
16	3.35	0.72	3.26	0.79	0.102
17	3.26	0.88	3.09	0.97	0.061
18	3.42	0.59	1.95	0.69	0.001
19	3.44	0.70	1.86	0.56	0.001
20	3.42	0.66	1.81	0.59	0.001
21	3.44	0.59	1.79	0.56	0.001
22	3.49	0.55	1.93	0.67	0.001
23	3.33	0.68	1.91	0.65	0.001
24	3.44	0.50	1.98	0.67	0.001
25	3.42	0.50	2.00	0.62	0.001
26	3.53	0.50	2.05	0.62	0.001
27	3.49	0.51	2.19	0.63	0.001
28	3.58	0.50	2.35	0.72	0.001
29	2.33	0.57	4.28	0.91	0.001
30	2.23	0.78	4.28	0.93	0.001

ical benefit in terms of pain. The improvement in pain relief was significant ($p < 0.001$, Wilcoxon test) with a mean Wong-Baker score pre and post-treatment 4.33 (SD=0.71) and 0.98 (SD=0.41), respectively. Throughout all the items of Hamilton scale, pre and posttreatment, showed significant differences (Wilcoxon test, $p < 0.001$), as shown in Table 1. Moreover, concerning the QLQ-C30, in all items except items 15-17, there was a significant improvement ($p < 0.001$) (Table 2).

Discussion

We believe that this prospective study is the first to report the results of a combination of radiotherapy with escitalopram in bone metastatic

cancer depressed patients. This drug appears to have a clinically relevant effect on pain relief. Overall, a safe toxicity profile for the combined treatment was observed.

Guidelines [19-21] recommend SNRIs as first or second line treatment in neuropathic pain, whereas SSRIs are not mentioned as a standard treatment. SSRIs have been tested in much fewer patients than the SNRIs. Thus escitalopram with its action on central pain inhibiting pathways might be effective in individuals with involvement of central pain modulatory systems [22]. Findings from Mazza et al. [23] demonstrated that escitalopram and duloxetine (SRNI) had no differences in terms of efficacy and safety in the management of chronic low back pain. No significant differences were observed between the two drugs on the reduction of weekly mean 24-h average pain as endpoint. Both escitalopram and duloxetine demonstrated significant improvement on Clinical Global Impressions of Severity (CGI-S) and the 36-item Short Health Survey (SF-36) measures. According to Perrot et al. [24] SSRIs seem to have modest analgesic effects and higher doses are required to achieve analgesia. Due to this reason, Mazza et al. [23] decided to use the dosage of 20 mg/day, which is the same that we have used. Moreover, Kroenke et al. [25] have shown that optimized antidepressant therapy followed by a pain self-management programme resulted in substantial improvement in depression as well as moderate reduction in pain severity and disability in primary care patients with musculoskeletal pain.

The most important endpoints in the palliative setting are symptom palliation and improvement of QoL [26]. The main endpoint of our study was to evaluate the pain relief with escitalopram in combination with radiotherapy, assessed with the Wong-Baker Rating Scale. Two secondary endpoints were also evaluated: QoL according to the RTOG-EORTC quality-of-life self-questionnaire (QLQ-C30 v 3.0) and the status of depression according to Hamilton Scale.

The EORTC QLQ-C30 is a subjective multidimensional tool used to evaluate the QoL of cancer patients. It consists of 30 questions incorporating 5 functional scales (physical, role, cognitive, emotional and social functioning), 3 symptom scales (fatigue, pain, nausea and vomiting), and a global healthscale. The remaining items assess other symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation and diarrhea), as well as perceived finan-

cial difficulties associated with the disease and its treatment [27-30]. The QLQ-C30 has been used to monitor treatment response [31-34], while in some other studies [35-44] the questionnaire has been used to evaluate the relief in different radiotherapy treatment schedules. In our study the QLQ-C30 showed significant differences in almost all of the items, except the items related to vomiting, constipation and diarrhea (items 15-17), which were unaffected by the combined treatment of radiotherapy and escitalopram. This was almost expected since the combined treatment obviously did not have any effect on stool or gastric disturbances. However, the effect of combined therapy in nausea might be related to the improvement of pain relief and the relevant decrease of the use of narcotics which normally have an effect on nausea.

The Wong-Baker FACES Pain Rating Scale is a pain scale that was developed by Donna Wong and Connie Baker. The scale shows a series of faces ranging from a happy face at 0, "No hurt", to a crying face at 10 "Hurts worst". The patient must choose the face that best describes how is feeling [45]. In our study the Wong-Baker Scale managed to assess a significant response to treatment in terms of pain relief. All patients presented at least a partial pain relief, while in 4 cases the pain relief was complete (Wong-Baker score=0). Beyond this, the Wilcoxon test showed significant overall improvement of our patients, which should not be underestimated.

The Hamilton Rating Scale for Depression (HRSD), also known as the Hamilton Depression Rating Scale (HDRS) or abbreviated to HAM-D, is a multiple choice questionnaire used to rate the severity of a patient's major depression [46]. The questionnaire rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss. Each question has between 3-5 possible responses which increase in severity, making this scale quite suitable for patients under depression [15, 16, 46-52]. In this study the HAM-D showed a significant improvement in all patients. This result was more or less easily predictive since escitalopram is mainly an anti-depressive drug.

In our trial this drug has shown a clear clinical benefit as adjunct treatment of bone metastasis. The primary outcome measure of pain was statistically significant. The QoL and depression also improved significantly. The alleviated symptoms and accelerated recovery in our patients may have been related to escitalo-

pram and we believe that it may be an effective medicine against neuropathic pain. The present study provided a rationale for the clinical application of escitalopram in selective bone metastatic and depressed cases in combination with radiotherapy. Also, this study highlighted the various symptom profiles and baseline QoL scores in patients referred for palliative radiotherapy to various skeletal metastatic sites in combination with escitalopram.

Our study is not without limitations. It is difficult to determine the etiology of the reported symptoms, as they could originate from disease, treatment(s), or both.

Another limitation of this study was that the patients have been under radiotherapy for highly painful sites, although many of them had multiple sites of bone disease or metastases that could contribute to their QLQ-C30 profile. Moreover, the inclusion of radiotherapy in the combined

treatment had obviously a tremendous effect in the palliation of symptoms. Thus, we don't know to which extent the pain relief and improvement of QoL and depression was related mainly to the irradiation or to escitalopram or vice versa. A randomized trial with more patients comparing radiotherapy vs radiotherapy plus escitalopram could provide more clear conclusions.

Conclusions

This study has shown that the combination of radiotherapy and escitalopram could be an approach to more efficient bone pain relief. The findings of this study can be inscribed into a wider randomized trial. Given that the small sample size and the lack of randomization represent limitations of this study, further studies on larger patient cohorts may establish the efficacy and uncover the limitations of this regimen.

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