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ORIGINAL ARTICLE

The management of painful bone metastases with biphosphonates and palliative radiotherapy: a retrospective evaluation of 372 cases

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Summary

Purpose: *The objective of this study was to evaluate the palliation of pain of bone metastases with biphosphonates and different radiotherapy protocols in 372 cancer patients.*

Patients and methods: *Patients were treated with one of the 3 different radiotherapy protocols: 30 Gy in 10 fractions (group A), 20 Gy in 5 fractions (group B) and 8 Gy in a single fraction (group C). Two patient groups were studied: one with radiotherapy alone and the second with biphosphonates plus radiotherapy. The severity of pain was recorded before treatment. According to the pain relief, two different groups were defined: palliation rate < 50% (limited palliation) and > 50% (partial palliation), including complete pain relief.*

Results: *Overall limited and partial palliation rates were 20.2 and 79.8%, respectively (complete pain palliation 24.2%). In the group treated with both external radiotherapy and biphosphonates, limited and partial palliation rates were 19.5 and 80.4%, respectively (p=0.47). For 244 metastatic lesions treated with palliative radiotherapy alone, limited palliation rate was 20.4% and partial palliation rate 79.5%. No differences were detected between the groups with or without biphosphonates treatment in terms of pain palliation. According to the radiotherapy protocol, limited palliation rates in groups A, B, and C were 17.7, 20.3, and 28.5%, respectively (p=0.19, p=0.38, and p=0.26, respectively). Partial palliation rates were 82.2% in group A, 79.6% in group B and 71.4% in group C (p=0.42, p=0.21, and p=0.11, respectively). Similarly, no statistically significant differences were detected among the 3 radiotherapy schemes in terms of pain palliation.*

Conclusion: *When combined with palliative radiotherapy, biphosphonates did not have any additive effects on pain palliation in the management of painful bone metastases. In addition, a single radiotherapy fraction provides equal pain palliation as multiple fractions.*

Key words: biphosphonates, bone metastases, pain, palliative radiotherapy

Introduction

In malignant diseases, the most frequent sites of metastasis are the lung, liver and bone. Bone metastases are found in around 65% of advanced cancer patients [1]. Due to their high incidence rates and their long survival times, prostate and breast cancers are two malignancies where bone metastases are frequently detected. Bone metastases are clinically important due to their complications which affect negatively the quality of life, such as pain, pathologic fracture, spinal cord compression, restriction of movements, neurological complications, suppression of bone marrow, anxiety and hypercalcemia [2-4].

The management of bone metastases should be multidisciplinary and the first objective is to eliminate the complications and improve patient's quality of life. The treatment to be chosen should be based on the general condition of the patient and the prognosis of the primary disease. Pain is the symptom most observed in bone metastases [5,6] and the most efficient treatment method in achieving pain palliation is radiotherapy. Generally, the indication for radiotherapy is present in all localized symptomatic bone metastases. The dose and fractionation to be applied have been discussed for years and no standard protocol recommendation exists.

Today, apart from radiotherapy, biphosphonates are widely used in the treatment of bone metastases. In

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most studies, it has been shown that biphosphonates significantly delay and prevent morbidities due to bone metastases [7-10]. In the management of painful bone metastases, the role of biphosphonates is not clear. The results of some studies suggest that biphosphonates are active in pain palliation [11-14]. Knowledge and current guidelines do not recommend biphosphonates for pain management in bone metastases as first line treatment in place of radiotherapy [15,16].

The aim of this study was to investigate the pain palliation in bone metastases treated with biphosphonates and different radiotherapy protocols in 372 cancer patients

Patients and methods

Patient and bone lesions characteristics

The median patient age was 56 years (range 25-89), and 153 (41.1%) were females. The median follow-up time was 5 months (range 1-60). Karnofsky performance status was recorded before treatment and all patients had at least 60% score. The origin of metastatic disease was as follows: lung cancer 33.1%, breast cancer 26.9%, prostate cancer 7.3%, gastrointestinal cancer 3.8%, unknown primary 16.4% and other systems 2.6%. Radiologically, 311 (83.6%) metastatic lesions were osteolytic, 28 (7.5%) osteoblastic and 33 (8.8%) of mixed type. Patients were evaluated in terms of treatment-dependent toxicities and grading was carried out according to the World Health Organization (WHO) criteria.

Radiotherapy alone

Palliative radiotherapy was delivered to 372 different metastatic lesions from 372 patients between 1997-2003 and treatment response was evaluated retrospectively. Patients were treated either by Cobalt-60 Teletherapy (Theratron 780-c AECL) or Linear Accelerator (Philips SL-25) with one of 3 different radiotherapy protocols: 30 Gy in 10 fractions (group A), 20 Gy in 5 fractions (group B) and 8 Gy in a single fraction (group C).

Radiotherapy plus biphosphonates

Palliative radiotherapy plus biphosphonate treatment was applied to 128 metastatic sites. In 47 of them oral clodronate (800 mg twice a day) was used, whereas in 81 i.v. pamidronate (90 mg / monthly) or zoledronic acid (4 mg / monthly) were administered. Two hundred and forty-four metastatic lesions were treated with radiotherapy alone.

Pain evaluation

Before treatment, pain evaluation was done subjectively using verbal descriptive scale and according to their pain severity patients were classified into 4 groups: 0: no pain; 1: mild pain; 2: moderate pain; 3: severe pain. The rates of mild, moderate and severe pain were 4.8 (18 lesions), 8.3 (31 lesions) and 86.8% (323 lesions), respectively. Before treatment, analgesic drugs (non steroid anti-inflammatory and opioids) were prescribed in 96.2% of the patients. According to the pain response rates, two groups were defined: response rate < 50% (limited palliation) and > 50% (partial palliation), including complete pain palliation.

Statistical analysis

In statistical analysis, the differences between the rates of categorical variables were evaluated by x^2 and Fisher's exact tests. A p-value < 0.05 was accepted as statistically significant.

Results

Overall limited and partial palliation rates were 20.2% (75/372) and 79.8% (297/372), respectively. Partial and limited palliation rates of patients treated with radiotherapy plus biphosphonates were 80.4% (103/128) and 19.5% (25/128), respectively. In oral clodronate treatment, the partial and limited palliation rates were 78.2% (36/46) and 21.7% (10/46), respectively. The pain palliation of 82 metastatic lesions treated with i.v. biphosphonates (pamidronate or zoledronic acid) were evaluated separately; partial and limited palliation rates were 81.4% (66/82) and 18.5% (15/82), respectively. Partial and limited palliation rates of patients treated with radiotherapy alone were 79.5% (194/244) and 20.4% (50/244), respectively. When pain palliation rates were compared according to the type of biphosphonates (oral clodronate vs. i.v. pamidronate / zoledronic acid), no statistically significant differences were detected (p=0.40). Similarly, there was no statistically significant difference in pain palliation rate between patients who received or not biphosphonate treatment (p=0.47; Table 1).

Furthermore, in radiotherapy group A, limited and partial pain response rates were 17.7% (29/163) and 82.2% (134/163), respectively. Limited and partial palliation rates in group B were 20.3% (29/167) and

79.6% (33/167), respectively, and in group C they were 28.5% (12/42) and 71.4% (30/42), respectively. Comparison of pain palliation rates among the 3 treatment protocols showed no statistically significant differences (p=0.298; Table 2).

All patients were evaluated for pain palliation and side effects one week, one month and every 3 months after palliative radiotherapy. The median duration of pain palliation was 7.03 months (range 1-60). Fifty-seven and 42.7% of the treated lesions had at least 2- and 3-month duration of pain palliation, respectively. Twenty-seven, 15.1 and 8.9% of the treated lesions had at least 6-, 12- and 18-month pain palliation, respectively. Six percent and 3.2% of the treated lesions had at least 24- and 36- month duration of pain palliation. Only 0.5% of the treated lesions showed a 60-month palliation of the pain. No significant difference between the radiotherapy protocols (p=0.101) or the groups that received or not biphosphonate treatment was detected (p = 0.26).

As for the side effects, nausea was observed in 3 patients during radiotherapy (moderate in severity and controlled by antiemetic drugs). Hypotension was observed in one case among the patients who received i.v. biphosphonate.

Discussion

Today biphosphonates are an important component in the management of bone metastases. There is a trend of administering biphosphonates before the delivery of palliative radiotherapy in bone metastases [17]. Many trials showed an important and remarkable reduction of skeletal-related events by biphosphonates, such as pathological fracture, spinal cord compression, hypercalcemia and need for palliative radiotherapy or orthopedic interventions [9-14]. Despite the absence of randomized data comparing biphosphonates with radiotherapy for pain palliation in some studies biphosphonates were found to be active in controlling pain and decrease the need for palliative radiotherapy to bone metastases [13-18]. The role of biphosphonates alone or in combination with radiotherapy in pain relief for bone metastases is still uncertain. An open-label randomized study was performed by van Holten-Verzantvoort et al. with oral pamidronate vs. control in women with bone metastases from breast cancer [19]. The pamidronate group had a reduction in severe pain by 30 %. In another trial Lipton et al. found that pamidronate significantly decreased the mean pain scores compared with the placebo group [20]. In a randomized, placebo-controlled trial conducted by Kohno et al. it was reported that zoledronic acid significantly reduced the mean pain score in patients with bone metastases from breast cancer [8]. In a meta-analysis by Wong and Wiffen in the Cochrane Library on biphosphonates for the relief of pain secondary to bone metastases, 30 randomized trials were examined [16]. The authors reported that there was evidence to support the effectiveness of biphosphonates in providing some pain relief for bone metastases. In our study, 128 painful bone metastatic lesions were treated with both biphosphonates and palliative radiotherapy. Overall partial and limited pain palliation rates were 80.4 and 19.5%, respectively. This result is similar to 244 painful bone metastatic sites treated with radiotherapy alone (partial and limited palliation rates were 81.4 and 18.5%, respectively). No statistically significant differences were detected in pain palliation rate between the two treatment schemes (p=0.47). This finding demonstrates that biphosphonates did not have any additive effect for pain palliation when combined with external radiotherapy and did not influence the response of pain in the management of painful bone metastases.

Radiotherapy is known as the most effective treatment for bone metastases. However, there are no standard recommendations about the optimal dose and fractionation scheme. Tong et al. reported on the efficacy of palliative radiotherapy in 1016 patients with bone metastases [21]; they compared 40.5 Gy in 15 fractions, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 15 Gy in 5 fractions and 25 Gy in 5 fractions. No differences were detected among the 5 radiotherapy schemes in terms of pain palliation. Similarly, in many randomized clinical

Table 1. Pain palliation rates according to the treatment modality

Treatment modality	*Limited palliation %*	*Partial palliation %*	*p-value*
RT alone	20.4	79.5	
RT with BIP	19.5	80.4	
RT alone + RT with BIP	20.2	79.8	NS

RT: radiotherapy, BIP: biphosphonates, NS: non significant

Table 2. Pain palliation rates according to the radiotherapy protocols

Radiotherapy protocol	*Limited palliation %*	*Partial palliation %*	*p-value*
Group A	17.7	82.2	
Group B	20.3	79.6	
Group C	28.5	71.4	
All group categories	20.2	79.8	NS

For patient grouping see text
NS: non significant

studies, no superiority was shown among the palliative radiotherapy dose and fractionation schedules [22-27]. A number of studies, including 2 large metaanalyses published in 2003, demonstrated that a single fraction is as effective as multiple fractions for the treatment of painful bone metastasis [16,21,28]. However, many patients still receive multiple fractions in many radiotherapy centers [29]. In our study, overall limited and partial bone palliation rates were 20.2 and 79.8 % (with 24.2% complete pain palliation rate). Partial palliation rates were 82.2% in group A, 79.6% in group B and 71.4% in group C (p=0.42, p=0.21, and p=0.11, respectively). Limited palliation rates for groups A, B, and C were 17.7, 20.3 and 28.5%, respectively (p=0.19, p=0.38, and p=0.26, respectively). This finding is similar with other relevant studies.

Conclusion

When combined with palliative radiotherapy, biphosphonates did not have any additive effects on pain palliation and did not influence the response of pain in the management of painful bone metastases. In addition, a single radiotherapy fraction provides equal pain palliation as multiple fractions in the treatment of painful bone metastases.

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