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review

Radiotherapy in palliative treatment of painful bone metastases

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Background. *Pain caused by bone metastases is the most common symptom requiring the treatment in cancer patients. Bone metastases often present as the first evidence of disseminated disease, the most common primary sites being breast, prostate, and lung. Important in palliative treatment is to reach a maximal effect with the minimal treatment. The aim of palliation for cancer patients is to increase the quality of their remaining life.*

Conclusions. *The management of bone pain includes analgesics, local treatment (radiation, surgery) and systemic treatment (hormones, chemotherapy, radioisotopes and agents such as bisphosphonates). The treatment of bone cancer pain often requires a multidisciplinary approach. Radiotherapy remains the most important palliative treatment for localized bone pain. The treatment duration can generally be reduced to a single treatment with excellent and long-lasting palliative analgesic responses. The treatment should be individualized according to the patient's clinical condition and life expectancy.*

Key words: bone metastases; palliative treatment; radiotherapy

Introduction

Pain caused by bone metastases is the most common symptom requiring the treatment in cancer patients and they often present as the first evidence of disseminated disease.[1] About three quarters of patients with the end-stage disease will eventually need the pain management.[2] Bone metastases are common in patients suffering from many types of cancer with systemic dissemination, especially breast cancer, prostate and lung cancer, with the incidence of approximately 70%, 70% and 35%, respectively.[3] Lesions occurring in breast, lung, prostate and kidney comprise 80% of all metastases to bone.[4] Bone metastases are associated with considerable skeletal morbidity, including severe bone pain, spinal cord or nerve root compression, pathological fractures and hypercalcaemia.[5-9]

Although the skeleton receives only 10% of the cardiac output, metastases in the skeleton are very common as compared to metastases to other tissues receiving a far greater amount of the cardiac output.[10] The bone metastases are found almost invaria-

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bly in the red marrow, and the bones most frequently involved are those with a high proportion of red marrow.[5,11] Thus, more than 80% of bone metastases are found in the axial skeleton.[2,6]

Bone metastases can be of osteolytic types (increase bone destruction), osteosclerotic types (increase bone formation), or mixed types. Osteolytic metastases are the predominant types of lesions in most cancers, but a sclerotic appearance is seen in the majority of prostate cancer metastases.[5]

Pain caused by bone metastases or from the invasion of the tumour in the bone is frequently the first symptom for which the patients will seek advice.[7,12,13] In general, there are two types of pains in patients with bone metastases. The first type is a continuous pain and is usually described as a dull aching pain that increases in severity over time. The second type of bone cancer pain is movement-evoked, breakthrough or episodic and is more acute in nature.[14]

Important in the palliative treatment is to reach a maximal effect with the minimal treatment. In cancer patients with systemic metastases and thus limited life expectancy, the aim of palliation is to increase the quality of their remaining life.

Different modalities in palliative therapy of bone metastases

The treatment of bone metastases requires a broad approach.[15] The reduction of pain is its major goal. Also, of great importance are the prevention of possible fractures and the improvement of mobility.[1]

The management of bone pain includes analgesics, local treatment (radiation, surgery) and systemic treatment (hormones, chemotherapy, radioisotopes and agent such as bisphosphonates).[1,16] Therefore, the treatment of bone cancer pain often requires a multidisciplinary approach.[17]

Analgesics

The control of bone pain usually begins with analgesics used in a 3-step approach. To relieve mild to moderate pain non-opioid analgesics (the first step) are initially used. With persistence or increase in pain when using non-opioid analgesics only, the treatment progresses to utilize weak opioides (the second step) changing to higher doses or more potent opioids (the third step), if the pain persists or becomes more severe.[17-19] These more potent opioids have significant side effects (constipation and lethargy are particularly common).

To limit the dose of opioids and their side effects, radiotherapy and sometimes surgery (*i.e.* no evidence of metastatic disease elsewhere in the body with primary tumour control) are used for the treatment of localised metastases.[16-19]

Radiation therapy

Most commonly, radiotherapy is used to provide pain relief for the painful bone metastases. It is an effective and safe non-invasive palliative treatment.[17,18]

The radiation treatment includes the local radiation when the disease is localized and the systemic one in more diffusely disseminated disease. The systemic radiation takes account of half-body irradiation (HBI) and therapy with radioisotopes.[1]

Local radiotherapy

Radiotherapy remains the most important palliative treatment for localized bone pain.[20] A number of randomized trials have been carried out and substantial proportion

of them were done on highly selected populations of patients due to the varying clinical presentation of bone metastases.[20-22]

In these trials, radiotherapy was reported to produce a complete pain relief at one month in 25% of patients. A pain relief at least 50% (*i.e.* partial response) at one month was achieved in 41% of patients.[20] However, the transient pain flare is common after the palliative radiotherapy for osseous metastases.[23] Hird *et al.*[24] found out that patients treated with a single 8 Gy reported a pain flare incidence of 39% and, after using multiple fractions, 41%. A further studies are warranted to determine predictors and necessary preventive interventions.[23,24]

The prospective randomized trials compared the effect of a single fraction (mostly of 8 Gy) to different multifraction regimen and different single fraction irradiation doses to themselves.[20-22,25-42] It was important that – on general – a single fraction of 8 Gy is equivalent to multiple fractions in quality and duration of pain relief (Table 1).

However, there is still questionable, if 8 Gy is the optimal single fraction dose.[30] Results of at least two single institution clinical studies indicate that 8 Gy could be considered as probably the "lowest" single fraction dose to be used in palliative setting in the treatment of painful bone metastases, although the single fraction radiotherapy of 4 Gy should not be simply discarded due to its applicability in specific cases.[31,34]

The only difference between the single fraction and the multifraction regimen observed was in the rate of re-treatment and in the rate of the pathological fracture. More patients from a single fraction group require the re-treatment.[25,36,37,41] In spite of an opinion, that the decision to re-treat a patient might be influenced by other factors, *i.e.* physician bias[43], a systemic review of randomised trials and meta-analysis confirmed that the re-treatment rate and the pathological fracture rate were higher after the single fraction radiotherapy.[21,22] On the other hand, one must be aware that discrepancies may exist between meta-analyses and individual large randomized, controlled trials.[44] Therefore, the most recent randomised studies only are to be considered. However, they are still controversial. For example, Roos *et al.*[38] reported the results of a TROG 96.05 trial, where no statistically significant difference in the rate of re-treatment procedures, cord compressions or pathological fractures was observed across different treatment groups, whereas Foro Arnalot *et al.*[26] proved that the re-treatment was more frequent in the arm with a single fraction irradiation.

Jeremic *et al.*[45] were investigating the effectiveness of a 4 Gy single-fraction re-treatment regimen for painful bone relapse after previous single-dose radiotherapy with 4 Gy, 6 Gy and 8 Gy. It is of note that after the re-irradiation the response rate was 74% and 46% of responses was recorded in previously non-responding patients. There was no difference in response according to the initial dose.

Results of prospective randomized trials comparing two different multifraction radiation schedules also confirmed that the irradiation with fewer fractions was as effective as the more prolonged regimens. However, shorter radiation schedules were proved to be more convenient to the patient and of less cost to the society.[29,39,40,42]

In the cases when pain is the first symptom of developing paraparesis radiotherapy is of crucial importance. However, when the spinal cord compression is suspected, high-dose corticosteroids should be administered and whole-spine magnetic resonance imaging scan performed as soon as possible but not later than 24 hours from the start of neurological deficit. Definitive treatment for diagnosed cord compres-

Table 1. Results of published randomized controlled clinical trials on dose and fractionation pattern for palliation of painful bone metastases. (Only trials with more than 100 patients enrolled listed in the table)

Reference	Comparison*		Number of patients Randomised	Primary endpoint p-value**
Bone Pain Trial Working Party, 1999[25]	A: B:	8 Gy in 1 fraction *vs* 20 Gy in 5 fractions or 30 Gy in 10 fractions	761	n.s.
Foro Arnalot P *et al.*, 2008[26]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	160	n.s.
Gaze MN *et al.*, 1997[27]	A: B:	10 Gy in 1 fraction *vs* 22.5 Gy in 5 fractions	280	n.s.
Hartsell WF *et al.*, 2005[28]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	898	n.s.
Hirokawa Y *et al.*, 1988[29]	A: B:	25 Gy in 5 fraction *vs* 30 Gy in 10 fractions	182	n.s.
Hoskin PJ *et al.*, 1992[30]	A: B:	4 Gy in 1 fraction *vs* 8 Gy in 1 fractions	270	n.s.
Jeremic B *et al.*, 1998[31]	A: B: C:	4 Gy in 1 fraction *vs* 6 Gy in 1 fraction *vs* 8 Gy in 1 fraction	327	A<B: p<0.025 A<C: p<0.0019
Kaasa S et al., 2006[32]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	376	n.s.
Kirkbridge P *et al.*, 2000[33]	A: B:	8 Gy in 1 fraction *vs* 20 Gy in 5 fractions	398	A<B: p=0.03
Koswig S *et al.*, 1999[34]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	107	n.s.
Ma as A *et al.*, 2008[35]	A: B:	6 Gy in 1 fraction*** *vs* 8 Gy in 1 fraction***	118	A<B: p=0.0211
Nielsen OS *et al.*, 1998[36]	A: B:	8 Gy in 1 fraction *vs* 20 Gy in 4 fractions	241	n.s.
Price P *et al.*, 1986[37]	A: B:	8 Gy in 1 fraction *vs* 30 Gy in 10 fractions	288	n.s.
Roos DE *et al.*, 2005[38]	A: B:	8 Gy in 1 fraction *vs* 20 Gy in 5 fractions	272	n.s.
Quilty PM *et al.*, 1994[39]	A: B: C:	Hemibody irradiation 6 Gy in 1 fraction *vs* Local irradiation 20 Gy in 5 fractions *vs* 89-Sr 200 MBq	284	n.s.
Rasmusson B *et al.*, 1995[40]	A: B:	15 Gy in 3 fractions *vs* 30 Gy in 10 fractions	217	n.s.
Steenland E *et al.*, 1999[41]	A: B:	8 Gy in 1 fraction *vs* 24 Gy in 6 fractions	1171	n.s.
Tong D *et al.*, 1982[42]	A: B:	20 Gy in 5 fractions *vs* 40.5 Gy in 15 fractions	266	n.s.
Total			**6616**	

*Gy – unit of dose, Gray; **n.s. – not significantly different at the 5% level;
***patient were treated also with zolodronic acid.

sion– surgical decompression or urgent radiotherapy – should be initiated within 24 hours.[9,18] The early recognition of the *symptoms* and a prompt diagnosis are essential for the onset of the optimal therapy.[46]

In conclusion, the single-fraction radiotherapy of 8 Gy should be a standard management policy for patients with painful bone metastases.[32] In clinical practice, however, with a single fractions more frequently are irradiated the older patients; those with more weight loss and poor performance status or with progressive local disease and/or widely disseminated disease elsewhere in the body. Pelvis, long bones and chest wall are more frequent irradiated with single fractions.[47] Compared with multiple-fraction radiotherapy, single-fraction regimen is equally effective when quality of life measures are studied, but, for lower medical and societal costs. Therefore, single-fraction radiotherapy should be considered as the palliative treatment of choice for majority of cancer patients with painful bone metastases.[48,49]

Half-body irradiation (HBI)

HBI is used in patients with widely metastatic disease when large segment of the body is to be irradiated. With this technique the irradiation dose can be delivered as a single fraction or through several smaller fraction doses.[50,51]

Three types of HBI fields have been described.[52] They are as follows: *(1)* Upper half-body irradiation (UHBI) – irradiation field encompasses the area from the level of mastoid process to the level of the iliac crest (L4-L5 interface or the umbilicus); *(2)* Lower half-body irradiation (LHBI) – upper border of irradiation field is placed at the lower edge of the upper HBI field (L4-L5 interface) and the lower border at the ankles; and *(3)* Midportion-body irradiation (MBI) – irradiation field extend from the top of the diaphragm to the bottom of the obturator foramina.

To date, single-dose HBI was one of the safest, fastest and most effective palliative tools in the treatment of cancer pain.[52]

As not being without any toxicity, the irradiated patients require either a one-day hospitalization or close monitoring several hours after the procedure.[51] A comprehensive premedication program has proven to decrease the acute radiation syndrome to an acceptable level.

The effectiveness and the safety of the single-doses HBI of different dose levels in patients with multiple bone metastases were analysed in RTOG 78-10 study.[52] The most effective and harmless HBI regimen tested were 6 Gy-regimen for the UHBI and 8 Gy-regimen for the LHBI or MBI. The increase in dose was associated with an increase in toxicity such as pneumonitis in UHBI and gastrointestinal upset in the LHBI or MBI. The bone marrow toxicity was maximal at 2 weeks post-HBIand its regeneration was seen in 4 to 6 weeks. HBI was found to relieve pain in 73% of irradiated patients and in as much as 20% of thm the pain relief was complete. Over two thirds of all patients achieved better than 50% pain relief. The HBI pain relief was dramatic with nearly 50% of all responding patients doing so within 48 hours and 80% within one week from HBI treatment.[52]

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In comparison with single-dose HBI, fractionated HBI eliminates the need for the premedication or longer post-therapy

observation. Fractionated HBI proved to be safe, tolerable and effective. Five daily fractions of 3 Gy each is considered the standard HBI regimen. It also allows for an increase in the total dose when necessary.[53]

With the aim to find the fastest, most effective and economically favourable fractionated HBI regimen for symptomatic bone metastases, International Atomic Energy Agency conducted a multicentre randomise phase III trial. One-hundred-fifty-six patients with bone metastases of breast, prostate, lung and other cancer were grouped into three arms: *(1)* controls –15 Gy in 5 fractions over 5 days; *(2)* hyperfractionation – 8 Gy in 2 fractions over 1 day; and *(3)* accelerated – 12 Gy in 4 fractions over 2 days. The results indicated that for most tumour types (an exception was cancer of the prostate) two daily doses of 3 Gy delivered in 2 consecutive days were as effective as a 5-day regimen of 3 Gy-daily fractions.[51]

Radioisotopes

The radionuclide therapy for bone pain has been used for more than 30 years. Acting systemically, a targeted therapy with radioisotopes is indicated in the management of disseminated disease when the repeated local treatments would become impractical. The potential toxicity of systemic administration of radioisotopes is reduced by their relatively selective targeting of the tumour. For the efficacy of this treatment the proper selection of patients is of paramount importance.

The following radionuclides were used in the treatment of painful bone metastases: 32-P, 89-Sr, 186-Re, 188-Re, 153-Sm, 223-Ra and 117-Sn. Most studies with these agents have been conducted in prostate and breast cancer patients and the most widely used isotopes were 89-Sr and 153-Sm.[16,20,54]

Bone targeting relies upon the selective uptake and prolonged retention of radionuclide molecules at sites of the increased osteoblastic activity on the border between bone and osteoblastic metastases. Some radionuclides have natural affinity for metabolically active bone (such as 89-Sr and 223-Ra) whereas the others (153-Sm and 186-Re) form stable complexes with bone-seeking cations, such as phosphate and diphosphonate.

Strontium (89-Sr) is an element that behaves biologically like calcium. As a group II metal, strontium has a natural affinity for metabolically active bone. After the intravenous administration, 89-Sr is concentrated in bone in proportion corresponding to osteoblastic activity. Of the 89-Sr that is not concentrated in bone, the excretion is predominantly renal (about 80%) and about 20% through the gastrointestinal system. A 89-Sr therapy is recommended for the patients with moderate pain and reasonable life expectancy. Published data reported a pain relief in approximately 74% of patients. The onset of the pain relief is generally within 7-21 days post-therapy, with a mean duration of relief of about 6 months. Transient increase in bone pain (painful flare) may occur in the first 2-3 days after the treatment and is usually of mild intensity, easily controlled with analgesics. The toxicity of such treatment is limited to temporary myelosupression, which typically occurs 6 weeks after the therapy and continues during the next 6 weeks.[16,54]

Comparing the effectiveness of 89-Sr and external beam radiotherapy (local radiotherapy or HBI), no difference in the median survival (89-Sr – 33 weeks, external beam radiotherapy – 28 weeks) and in pain relief at 3 months (89-Sr – 66.1%, local radiotherapy – 65.9%, HBI – 63.3%) were observed between the three treatment modes. However, whereas the retreatment rates between 89-Sr and external beam radiotherapy were comparable, after 89-Sr treatment significantly fewer patients reported new

pain sites than after the local radiotherapy or HBI.[39] It was also reported that the addition of 89-Sr to local radiotherapy of painful bone metastases reduced the progression rate in endocrine resistant metastatic prostate cancer.[55]

Samarium (153-Sm) forms a stable complex with ethylenedinaminetetramethylene phosphonic acid (EDTMP). This phosphonate complex concentrates in the skeleton, in proportion that corresponds to osteoblastic activity. Together with beta-rays samarium emittes also gamma rays. After the intravenous administration, phosphonate complex has a rapid bone uptake and plasma renal clearance. A pain relief was observed in 62-74% of treated patients with higher overall response rates at higher doses. The response duration was about 8 weeks (range 4-35 weeks). The bone marrow suppression was generally mild and reversible, and pain flare was rare. 153-Sm is the most widely used radiopharmaceutical agent for palliation of bone pain in the United States.[16,54]

In the therapy with radionuclids two rhenium isotopes, 186-Re and 188-Re have been used. They belong to group of beta-emitters. Several initial studies reported the safety and efficacy of using rhenium isotopes. In the study of Piffanelli *et al.*[56] no differences was found between 186-Re and 89-Sr concerning the response rate which was not related to patients' age, skeletal extension of tumour, evidence of non-bony metastases, previous chemotherapy and/or external-beam radiotherapy. However, osteolytic lesions responded worse than osteoblastic or mixed ones. Haematological toxicity (mild to moderate), mainly affecting platelets, was observed in 25.5% of all treatments and in 38.9% of retreatments.

The Cochrane review of four randomised trials showed that radioisotopes might completely abolish pain over one to six months with no increase in the analgesic use; adverse effects, specifically leukocytopenia and thrombocytopenia, had also been experienced.[57] Thus palliation of bone pain with radioisotopes is indicated as a complementary therapy to other treatment modalities in context of an interdisciplinary pain management.[58] While the external beam radiotherapy remains the mainstay of pain palliation of solitary bone lesions, bone-seeking radiopharmaceuticals have a role in selective cases with multiple osseous metastases.[59]

Table 2. Commonly used indications for surgical treatment of pathologic bone fractures and impending fractures (prophylactic fixation) in patients with bone metastases

Pathologic fractures
Expected survival longer than 6 weeks
No greater benefit from nonoperative treatment
Ability to obtain internal stability
Patients condition permits operation
Early mobilization possible
Impending fractures
Metastasis in weight-bearing bones
Lytic lesions with a diameter >2-3 cm or with cortical destruction > 50%

Surgery

In the case of pathologic fractures, there are two local therapeutic options available, including radiotherapy and/or surgery. For the surgical treatment commonly used indications are also impending fractures (Table 2).[1] In selected cases, the implementation of new minimally invasive procedures (*i.e.* MR-guided focused ultrasound surgery and percutaneous polymethylmethacrylate vertebroplasty) that offer a remarkable advantage of effective and immediate pain relief with few complications, should be considered.[17,60,61]

Malignant spinal cord compression asks for the most urgent surgical intervention.

Table 3. Bisphosphonates approved for the treatment of breast cancer patients with bone metastases[3,67]

	Relative potency	Dose (mg)	Schedule	Mode of administration
Non-nitrogen				
Clodronate	1	1600	daily	oral
Single-nitrogen				
Pamidronat	20	90	every 3-4 weeks	2 hours *i.v.*
Ibandronat	857	6	every 3-4 weeks	1 hour *i.v.*
		50	daily	oral
Two nitrogens				
Zolendronic acid	16700	4	every 3-4 weeks	15 min *i.v.*

The decision on treatment modalities or combination of different therapies (surgery with postoperative radiotherapy, radiotherapy only, specific therapies according to tumour type) should be carried out on multidisciplinary setting according to the neurological, oncological, orthopedical and systemic principles.[9]

Bisphosphonates

Bisphosphonates are synthetic analogues of naturally occurring pyrophosphate compounds that inhibit calcification.[62] They bind preferentially to bone at sites of active bone metabolism and are released from the bone matrix during bone resorption. Potently they inhibit the osteoclast activity and the survival, thereby reducing the osteoclast-mediated bone resorbtion.[63] Results of *in vitro* studies have shown that bisphosphonates inhibit tumour cell adhesion and invasion of the extracellular matrix. They also induce tumour-cell apoptosis.[64,65]

Bisphosphonates are used in treatment of many disorders, such as metabolic bone disease, Paget´ disease, osteoporosis and metastatic bone disease. They have also shown the efficacy in the cancer treatment-induced bone loss.[62,66]

Bisphosphonates have emerged in recent years as a highly effective therapeutic option for the prevention of skeletal complications secondary to bone metastases. The clinical benefits of the bisphosfonate therapy have been evaluated in many clinical trials. The majority of these trials used a composite end point defined as a skeletal-related event (SRE) or bone event, which generally includes events such as pathologic fracture, radiation to bone, surgery to bone spinal cord compression and hypercalcaemia due to underlying malignancy.[3,20,67,68]

Bisphosphonates have become the current standard of care for preventing skeletal complications associated with bone metastases. There are several bisphosphonates that are used for the treatment of patients with bone metastases from breast cancer (Table 3).[67] Zoledronic acid, pamidronate, clodronate and ibandronate all have demonstrated the efficacy superior to that of placebo in patients with breast cancer.[3,69] The efficacy of zoledronic acid and pamidrinate was compared in randomized fashion and the former was shown to be significantly more effective at reducing the risk of an SRE.[3,70]

Zoledronic acid and ibandronate were also shown to exert synergistic antitumour activity when combined with various specific anticancer treatments such as chemotherapy, hormone therapy, radiotherapy or monoclonal antibodies.[71-74] However, due to potential nephrotoxic effect of *i.v.* bisphosfonates, chemotherapy noxious to the kidneys should not be administered on the same day as bisphosphonates.[66]

Conclusions

Relieving bone pain in cancer patients is integral and crucial part of the comprehensive cancer management. Radiotherapy is an important mode for the local and systemic pain relief. It effectively decreases morbidity caused by painful bone metastases, resulting on substantial improvement of the quality of patient's life. No matter what kind of treatment modality or their combinations is planned to be applied, it should be tailored according to the patient's clinical condition and life expectancy.

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