Management of Bone Pain Secondary to Metastases

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Citation

N Senior Resident, F Patel, S Sharma. *Management of Bone Pain Secondary to Metastases*. The Internet Journal of Oncology. 2007 Volume 5 Number 1.

Abstract

Bone pain secondary to metastases decreases the quality of life of the patients who have a relatively longer survival. For the purpose of pain relief in bone metastases available modalities include analgesic drugs, radiation therapy, corticosteroids, nerve blocks, radiopharmaceutical agents, biphosphonates and surgical procedures. Analgesic drugs should be prescribed in all patients as per the WHO guidelines. Palliative single fraction radiotherapy to the appropriate target volume is recommended for metastatic bone pain relief. Radionuclide therapy is used for multifocal painful bone metastasis both above and below the diaphragm where increased uptake in painful lesions is demonstrated on bone scan. Bisphosphonates ease the symptoms of bone metastases by decreasing the activity of osteoclasts. Surgical intervention is required for patients with non vertebral metastatic lesions > 2.5 cm in diameter or with lesions located in weight bearing areas. Thus treatment needs to be individualized for adequate pain relief.

INTRODUCTION

Although more than half of all cancer patients can look forward to long-term disease-free survival, there are still thousands of cancer patients whose disease progresses to a stage where cure is no longer feasible. Treatment options referred to as “palliative care” must then be considered. The objective of palliative care is to maximize survival time, or to decrease pain and suffering, thereby enhancing the remainder of the patient's life. Palliative care may involve surgery, chemotherapy, radiation therapy, or other approaches to managing advanced cancer. Pain is one of the most distressing symptoms of patients with advanced cancer [1].

Metastatic involvement of the bone is one of the most common cause of pain in cancer patients. Thirty to 70% of all cancer patients develop skeletal metastasis at some point of their disease. The most common primary malignancies that metastasize to the bone are breast, kidney, lung and prostate. The most common site of metastasis are the vertebrae, pelvis and long bones [2]. Pain is the most common symptom of bone metastasis and develops gradually over weeks to months, becoming progressively more severe. Pain combined with other complications (eg. hypercalcemia, pathological fracture, nerve root compression, focal neurological defecits and forced immobilization) can lead to decrease in patient's quality of life. Further the survival of patients with bone metastasis is prolonged because these lesions are rarely the cause of death [3].

Although the bone scan is adequate for screening most patients with known malignancy and bone pain, additional plain radiographs of symptomatic areas are indicated, since pure lytic lesions may not present as increased uptake on bone scan. If plain radiographs demonstrate a lytic lesion inspite of negative bone scan, a full body bone survey is recommended to determine the extent of metastasis. MRI of the spine is superior to any other imaging study to detect epidural tumor associated with vertebral body metastasis with potential for either spinal cord/ nerve root compression [4].

Treatment options available for pain control in this patient population include analgesic drugs, radiation therapy, corticosteroids, nerve blocks, radiopharmaceutical agents, biphosphonates and surgical intervention. Analgesic therapy is effective for the majority of patients with bone metastases. Analgesic drugs include nonopioid analgesics, opioid analgesics, and adjuvant analgesics. Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful for mild to moderate pain and work synergistically with opioids. NSAIDs are relatively inexpensive and are widely available. They are used in all patients with painful bone metastasis if no contraindications to NSAID therapy exist. Opioids are an integral part of the analgesic regimen for cancer patients. Opioids are effective, easy to administer, cause no damage to any major organ system, have no ceiling effect, and

usually provide adequate pain relief with acceptable side effects. Adjuvant analgesics include antidepressants, anticonvulsants and local anesthetics and can be added to enhance non opioid and opioid analgesia [5] .

Patients with bone metastases comprise the largest group of patients receiving palliative radiation therapy. Local field radiation therapy is used for patients with limited and uncomplicated bone metastasis while systemic radiation therapy using wide field radiation therapy or radionuclide therapy is used for patients with multiple bone metastases, often after failure of local field treatment, usually in patients with short life expectancy. Some degree of pain relief occurs in around 70-80% of patients. Pain relief usually lasts for about 2/3 rd of the patients remaining life [6] . When the treatment objective is pain relief, a single 8 Gy treatment prescribed to the appropriate target volume is recommended as the standard dose fractionation schedule for the treatment of symptomatic and uncomplicated bone metastasis in previously non- irradiated areas [7] .

A dose-response relationship can be established for local control of a variety of malignancies treated with radiation, yet palliation of symptoms often does not have a clear dose-response relationship. Protracted radiation schedules are not warranted in such patients except in special clinical situations. Palliation with radiation therapy is achieved quite promptly, with minimal side effects and a very small risk of any long-term consequences in patients who have a limited life expectancy [8] .

In the meta analysis on the dose fractionation radiotherapy trials by the cancer care Ontario group: 2 trials comparing single versus single fraction (4Gy vs. 6Gy vs. 8Gy), 8 trials comparing single versus multiple fractions (8Gy vs. 20Gy/5F, 24Gy/6F, 30Gy/10F; 10Gy vs. 22.5Gy/5F) and 6 trials comparing multiple versus multiple fractions (20Gy/5F vs. 30Gy/10F, 15Gy/3F vs. 30Gy/10F, 25Gy/5F vs. 30Gy/10F, 20Gy/10F vs. 22.5Gy/5F vs. 30Gy/15F, 20Gy/2F vs. 24Gy/6F, 20Gy/5F vs. 40Gy/15F, 15Gy/5F vs. 20Gy/5F vs. 25Gy/5F vs. 30Gy/10F) were included. The meta analysis showed no significant difference in complete and overall pain relief between single and multifraction palliative radiotherapy for bone metastasis [9] .

In the randomized trials reported by the Dutch Bone Metastasis Study Group comparing 8Gy/F to 24Gy/6F, of the nine randomized trials comparing single versus multiple fractions, eight reported no difference in pain relief or duration of relief with single fraction compared to fractionated regimen [10] .

According to the RTOG report, frequency of re-treatment was greater in patients assigned to lower doses but this did not make a great difference in response rate. Trials comparing SF to MF regimens have reported higher frequency of retreatment in the SF groups. Re-irradiation should be considered when there is no pain relief or pain progression after radiotherapy, partial response with initial radiotherapy and the hope of achieving further pain reduction with more radiotherapy and partial or complete response with initial radiotherapy but subsequent recurrence of pain. However, although response to first course of retreatment is good, response to second or third retreatment is disappointing [11] .

Wide field radiotherapy (WFRT) of patients with widespread metastasis, usually with 4-6 weeks interval between the WFRT can be used as primary palliative therapy (to allow recovery of blood counts). WFRT can be used as primary palliative therapy for widespread bone metastasis not well controlled with analgesics, age 75 years or younger, KPS>70, adequate bone marrow, renal, hepatic and cardiac reserve and life expectancy more than six weeks. WFRT is delivered using 8-10 MV radiation through anterior-posterior portals, with extended SSD, blocks, bolus and compensators. Dose for upper hemibody is 6Gy and for lower and middle segment is 8Gy [12] .

WFRT in fractionated doses at 3Gy/1wk to a total dose of 15Gy have been used to deliver a higher total dose to increase the efficacy of treatment. Toxicities were comparable and the benefit was much greater for the higher dose group. WFRT provides pain relief of 64-100% with complete relief of 8-76% for single fraction regimens and 49-86% for fractionated regimens [13] .

RTOG 82-06 compared half body irradiation added to local irradiation versus local irradiation alone and showed that adjuvant WBRT delayed the progression of existing disease and prolonged the median time to appearance of new lesions. There was also a survival benefit at 1 year (44% versus 33%) [14] .

Radionuclide therapy is recommended for adult patients with uncomplicated multifocal painful bone metastasis above and below the diaphragm whose pain is not controlled with conventional analgesics and where increased uptake in painful lesions is demonstrated on bone scan. This involves administration of a bone seeking isotope which will be

concentrated in bone metastasis at sites of increased osteoblastic activity. The isotopes deliver their radiation dose by the release of beta particles with a short range of a few mm thereby concentrating their dose within the area of uptake. The selection of patients should consider the patients marrow function, performance status, recent use of other marrow suppressive agents (chemotherapy or radiotherapy), unsuitability for alternative palliative interventions (WFRT, hormone therapy or chemotherapy) and life expectancy of > 6 weeks [15].

US FDA has approved two radionuclide agents (Strontium 89 and Samarium 153) for use in bone metastasis. Recommended dose of Sr 89 is 148 Bq (4mCi) and for Sm 153 is 37 mBq (1 mCi/Kg) given by slow i. v. injection. Patients with partial response or complete response following radionuclide therapy may be considered for repeat administration for persistent or recurrent bone pain. Complete pain relief from Sr 89 range from 0-43%. Onset of pain relief occurs at 10-20 days, median duration of pain relief is 12 weeks. The main toxicity is myelosupression with nadir seen at 4-8 weeks. Other radionuclides used in bone metastasis include Re 186, I 131, Sn 117 and P 32 [16].

Bisphosphonates are being increasingly used in patients with multiple bone metastases. Bisphosphonates work to slow the activity of osteoclasts, thereby preventing excessive bone loss (reabsorption) and the associated elevation of blood calcium levels. In this process, they ease symptoms, including fracture due to weak, thinning bones, as well as the range of symptoms associated with hypercalcemia. Bisphosphonates may be taken by mouth or given intravenously. Intravenous use is most common, as these drugs are difficult for the digestive system to absorb. Bisphosphonates are proving to be very useful since patients experience few side effects (generally only minimal flu-like symptoms) and only for a short period of time. Side effects of biphosphonates include nephrotoxicity and gastrointestinal intolerance. Etidronate, clodronate, pamidronate and zolendronic acid are available for clinical use [17].

Orthopaedic consultation is considered for patients with non vertebral metastatic lesions > 2.5 cm or with lesions located in weight bearing areas. Early prophylactic mechanical stabilization of such lesions provides improved pain control and better long-term ambulation compared with using stabilization when the pathological fracture has occurred. Metastatic lesions at greater risk of fracture are – occupying more than 50% diameter of the bone, present in weight bearing bones or predominantly osteolytic. Postoperative radiotherapy can usually commence within 48 hours of internal fixation in most cases [18].

CONCLUSION

Pain secondary to bone metastasis is common in the oncology patient population and when uncontrolled, seriously impacts a patient's quality of life. A systematic multidisciplinary approach to the diagnostic and therapeutic management of these patients can result in cost-effective, adequate pain control in the majority of these patients.

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