Advances in the Treatments of Metastatic Bone Pain

Qinglan Ren, Yongzhong Wu

Department of Oncology, College of Clinical Medicine, Chongqing University of Medical Sciences, Chongqing 400016, China

Abstract Management of metastatic bone pain is an important and difficult task. In the article reviewed the recent progresses of the main treatments of metastatic bone pain in four aspects: analgesics, radiotherapy, bisphosphonates, radionuclide, and hope it could be helpful to scientific researchers and clinic workers.

Key words Metastatic bone pain; Treatments

Introduction

Cancers commonly metastasize to bone, and up to 80% of breast, prostate, and lung cancer patients had bone metastases. The site and distribution of bone metastases, and skeletal complications such as pathologic fracture and spinal cord compression could affect the patient´s prognosis. Invasion to bone by a metastatic lesion is the most common cause of pain in bone metastases. the metastatic bone pain is the common complication which results in impaired mobility and reduced quality of life and has a significant negative impact on survival [1, 2]. Management of pain in these patients is an important and difficult task, and now it has become the hot study field, we review the advances in the treatments of metastatic bone pain as follows.

The treatment of analgesics

Analgesics which killing pain by three stages in conformity with the WHO are wildly used in clinic. If the pain is rated 1~3 on the pain scale, non-opioids are options, 4~6 scales, a weak-opioid will be the choice, if the pain is rated greater than 7, a strong-opioid will be given with dose titrated, or adjusted (either increased or decreased) until the pain is relieved. But these medicines all have side -effects. Side effects of non -opioid medicines such as acetaminophen (also called Tylenol) and NSAIDs such as ibuprofen and the COX-2 inhibitors vary, but in general, most NSAIDs are associated with gastrointestinal toxicity, such as ulcers and bleeding, they also slow blood clotting, so they must be used cautiously in patients with bleeding or clotting disorders. Opioids, the strongest pain relieving medicines, include oxycodone, morphine, fentanyl, and hydromorphone, all excellent medicines for the treatment of cancer pain. Opioids lead to such as respiratory depression, sedation,nausea, vomiting, and constipation, etc. Analgesics are important in palliative therapy, because they relieve pain while administering and awaiting the relief of pain from other treatments. Furthermore, analgesics will relieve persistent levels of pain if complete pain relief is not achieved with other ways. Noticely, Some people think that if their pain becomes severe, they will need to receive intramuscular (IM) injections or "shots". Actually, injections are not commonly used to relieve cancer pain. Giving medicines by mouth (oral administration) is recommended for most patients because it is convenient, well tolerated, and usually is the least expensive. In addition to pills, capsules or injections, there are other ways the medicine can be given: skin patch, rectal suppositories etc. Skin patch is a bandage-like patch which is placed on the skin that slowly but continuously releases the medicine through the skin for 2~3 days. One opioid medicine, fentanyl, is available as a skin patch. Giving medicine in this way is less likely to cause nausea and vomiting. Rectal suppositories, this type of medicine dissolves in the rectum and is absorbed by the body. When the pain occurs day after day, medicines are given on an around-the-clock (ATC) schedule to ensure that the body always has a supply. In the past, medicines were

Correspondence to: Qinglan Ren
Tel: 023-89012944
13206010867
Email: renqlwu@yahoo.com.cn

given only on an as needed basis, or PRN, with the patient waiting until they were in pain. This type of schedule allowed periods of severe pain. Around-the-clock dosing works better. This means giving the medicine on a regular basis, whether the patient is in pain or not. In some situations patients are instructed to take a pain medicine as needed. This is usually along with an ATC medicine that they are already taking. Sometimes we have to use Adjuvant analgesics. Adjuvant analgesics are medicines that have a purpose other than treatment of pain but help relieve pain in some situations. Adjuvant analgesics used to help relieve cancer pain include the following:Antidepressants,some antidepressants have been found to relieve pain as well as decrease depression, they may relieve neuropathic pain; Tricyclic antidepressants are one type that can be used, a prescription is needed for these medicines. Anticonvulsants:these medicines are generally used for seizure disorders and are useful in relieving tingling and burning pain, such as neuropathic pain. Steroids: Steroids may be used to relieve pain associated with swelling and with bone pain, a prescription is needed for these medicines.

Analgesics help a lot in controlling the metastases bone pain, but sometimes the clinical effect is not satisfactory if the pain is refractory to conventional analgesics, it cannot stop osteolysis which often leading to bone-marrow compression and pathological fractures, and metabolic disorders. So it is seldom used as the single method in clinical medical work.

The treament of radiotherapy

Bone metastaseis is one of the most common conditions requiring radiation therapy today. The main aim of the therapy is to relieve of bone pain, prevention of pathological bone fractures as well as its healing, with anticipated effect upon improving mobility, function, and quality of life. Wu JS *et al.*[3] carried out a research to characterise the effect of palliative radiotherapy treatment, outcomes was evaluated by the Brief Pain Inventory within a radiotherapy clinic. In the study, One hundred and nine ambulatory patients provided pre- and post-treatment pain assessments at 4~6 weeks after palliative radiotherapy. The self-administered Brief Pain Inventory questionnaire was completed by patients during their visits. Changes in pain and seven-item functional interference scores were analysed. They found that most of the patients had prostate (n=42) or breast (n=42) cancer. The mean Karnofsky performance score was 70 before palliative radiation therapy. Sixty-eight per cent of patients were treated with a single fraction (6~8 Gy) and 25% received 20 Gy/five fractions. The overall response (reduction in worst pain by > or = 2/10) was 72%. Sixty-one per cent of patients had stable or reduced consumption of opioid analgesics. A significant reduction for all seven functional interference items was seen after treatment, the greatest improvement being general activity (-2.4/10). There was significant correlation between pain reduction and improvement in functional interference. it was concluded that this quality assurance initiative showed that palliative radiotherapy reduced both pain and its interference on function among ambulatory patients with symptomatic bone metastases. The reduction in pain was correlated with reductions in functional interference. We know that the pathophysiology of bone metastases remains very complex, some reserchers[4] have found radiation will reduce the pressure in bone marrow by reducing the number of tumor cells, and the very rapid response to radiation treatment seen in some patients is probably related to the presence of highly radiosensitive inflammatory cells. This may be the part reason to explain why radiation treatment is very effective in reducing pain. For localized bone pain, external beam radiation therapy (EBRT) will be successful in reducing pain in some 80% of patients. However, optimal fraction dose and total doses of EBRT required for pain relief have been unknown. It has been reported recently that single fraction radiotherapy should be the standard dose schedule for all patients with painful bone metastases. The Randomized Dutch Bone Metastasis Study [5] observed the effect of a single fraction of 8 Gy versus 24 Gy in six fractions on painful bone metastases. The main purpose of the study was to analyze the palliative effect of radiotherapy in long-term surviving patients, and to identify prognostic factors for survival. Response rates were compared in all patients surviving >52 weeks. The Cox proportional hazards model stratified by primary tumour was used for

multivariate (MV) analyses of prognostic factors for survival. In 320 patients surviving >52 weeks, responses rates were 87% after 8 Gy and 85% after 24 Gy (P= 0.54). Duration of response and progression rates were similar. For all primary tumours, prognostic factors for survival were a good Karnofsky Performance Score, no visceral metastases, and non-opioid analgesics intake (all factors, MV P<0.001). They concluded that single fraction radiotherapy should be the standard dose schedule for all patients with painful bone metastases, including patients with an expected favourable survival. Other studies also proved that radiation treatment given in a single fraction is an efficient and cost-effective alternative to traditional multifraction radiotherapy courses.

The treatment of bisphosphonates

Several trials [6, 7] have confirmed the ability of bisphosphonates to reduce or delay these skeletal complication and the bony pain. Bisphosphonates are the current standard of care for preventing skeletal complications associated with bone metastases. Clinical trials investigating the benefit of bisphosphonate therapy have used a composite end point defined as a skeletal-related event (SRE) or bone event, which typically includes pathologic fracture, spinal cord compression, radiation or surgery to bone. Bisphosphonates have been shown to significantly reduce the incidence of these events in patients with bone metastases. Zoledronic acid (Zometa; Novartis Pharmaceuticals Corp.; East Hanover, NJ), pamidronate (Aredia; Novartis Pharmaceuticals Corp.), clodronate (Bonefos; Anthra Pharmaceuticals; Princeton, NJ), and ibandronate (Bondronat; Hoffmann-La Roche Inc.; Nutley, NJ) all have demonstrated efficacy superior to that of placebo in patients with breast cancer. There are substantial differences among these agents in their potency, dose and route of administration, and side effects. Zoledronic acid is the only bisphosphonate that has been compared directly with pamidronate, and it was shown by multiple event analysis to be significantly more effective at reducing the risk of an SRE. In patients with prostate cancer, clodronate, etidronate (Didronel; Procter and Gamble Pharmaceuticals, Inc.; Cincinnati, OH), and pamidronate have demonstrated transient palliation of bone pain. However, zoledronic acid is the only bisphosphonate to demonstrate both significant and sustained pain reduction and a significantly lower incidence and longer time to onset of SREs compared with placebo. Zoledronic acid is also the only bisphosphonate to demonstrate efficacy in patients with bone metastases from a variety of other solid tumors, including lung cancer and renal cell carcinoma. In conclusion, bisphosphonates effectively reduce skeletal complications in patients with bone metastases and zoledronic acid has demonstrated the broadest clinical activity in patients with a wide variety of tumor types. Although they are not life-prolonging, bisphosphonates can be supportive therapy for patients with bony metastases. Clinical indicators of when the therapy should be started and stopped have not yet been determined , and they are not clear guidelines regarding the integration of bisphosphonate therapy with other methods or injuvant management. Despite their widespread use in metastatic bone disease, some bisphosphonate drugs are associated with adverse events (AEs), particularly renal toxicity, adding to treatment burdens and increasing healthcare costs. some open-label trial demonstrates that long-term use of intravenous bisphosphonates is well tolerated.

The treatment of nuclear medicine-based radionuclide

It is not a short time for nuclear medicine-based radionuclide therapy in the management of bone metastases pain. In comparison with analgesics, external beam radiotherapy, or other methods, it still appears to have lower priority among medical oncologists. It has been proved to be efficent to treat metastic bone pain. Ubieto MA *et al.*[8] reported that Sm153-EDTMP treatment is efficacious in patients with metastatic bone pain with effective response in 63.15% of the treatments. Other reserchers got the same results [9]. In the article of Damerla V *et al.*[10], recent developments in the use of radionuclides were broadly reviewed in the context of treatment paradigms, radionuclide toxicity, cost, and overall outcomes, and an impression of the use of radionuclides in metastatic bone disease was derived. Through a number of studies, they suggested that radionuclide therapy has been shown to be an efficacious

and cost−effective means of alleviating bone pain in metastatic disease. Moreover, its early use in pain therapy may limit cancer progression by inhibiting oligometastases. Thus, radionuclides can significantly decrease patient morbidity, increase patient survival, and perhaps attenuate the aggressiveness of cancer. Latestly, based on the concept of bifunctional radiopharmaceuticals, some scientists developed a highly stable (186)Re−mercaptoacetylglycylglycylglycine (MAG3) complex − conjugated bisphosphonate, [[[[(4 −hydroxy −4,4 − diphosphonobutyl) carbamoylmethyl] carbamoylmethyl] carbamoylmethyl]carbamoylmethanethiolate]oxorhenium (V)((186)Re−MAG3−HBP) for the treatment of painful bone metastases. previous studies have proved that this agent showed a superior biodistribution as a bone−seeking agent in normal mice when compared with (186) Re−1−hydroxyethylidene−1, 1−diphosphonate ((186) Re−HEDP). Oqawa K *et al.* established animal models of mammary tumor, they observed when (186)Re − MAG3−HBP was administered, tumor growth was significantly inhibited. Allodynia induced by bone metastasis was attenuated by treatment with(186)Re−MAG3−HBP or (186)Re−HEDP, but (186)Re−MAG3−HBP tended to be more effective. These results [11] indicate that (186)Re−MAG3−HBP could be useful as a therapeutic agent for the palliation of metastatic bone pain. Some reserachers propose that physician education regarding radionuclide therapy be improved and additional investigations to evaluate newer radionuclides and treatment paradigms (eg. higher activities, repetitive or cyclic administration, chemosensitization, or chemosupplementation) be strongly encouraged.

Summary

Besides the methods listed above, there are other strategies involving in managing bone pain, for instance chemotherapy, surgery, etc. Bone pain palliation is critical for cancer patients afflicted by bone metastases, while the pathophysiology of bone metastases remains very complex, single department cannot slove it totally. It highlights the need for standardisation and co−ordination among researchers in cancer pain studies. Some scientific findings [12] have indicated that combined therapy of 89Sr−chloride and zoledronic acid in patients with painful bone metastases is more effective in treating pain and improving clinical conditions than 89Sr−chloride or zoledronic acid used separately. Using computed tomography−based or magnetic resonance imaging−based evaluations as objective methods for assessing therapeutic outcomes, some trials suggested that combined radiotherapy and ibandronate provided substantial bone pain relief and increased bone density [13]. Many articles highlights the need for standardisation and co−ordination among researchers in cancer pain studies. So a comprehensive and an interdisciplinary clinical approach are intensive recommended .The increase in survival has improved through a multimodal approach combining, inhibition of osteolysis, with prophylactic orthopaedic surgery and radiation therapy, etc. [14] The combination protocol of appropriate pain management needs further study. Data from clinical collaborations will help optimize therapy for pain palliation, increase its awareness among oncologists, and contribute effectively to patient palliation and quality−of−life improvements.

REFERENCES

1. Janjan N. Bone metastases: approaches to manage ment. Semin Oncol, 2001 Aug, 28: 28−34.
2. Delea T, Langer C, McKiernan J, *et al.* The cost of treatment of skeletal−related events in patients with bone metastases from lung cancer. Oncology, 2004, 67:90−396.
3. Wu JS , Monk G, Clark T, *et al.* Palliative radiotherapy improves pain and reduces functional interference in patients with painful bone metastases: a quality assur ance study. Clin Oncol (R Coll Radiol), 2006 Sep, 18: 539−544.
4. Vakaet LA, Boterberg T. Pain control by ionizing radiation of bone metastasis.Int J Dev Biol, 2004, 48:599−606.
5. Van der Linden YM, Steenland E, van Houwelingen HC, *et al.* Patients with a favourable prognosis are equally palliated with single and multiple fraction radio therapy: results on survival in the Dutch Bone Metastasis Study.Radiother Oncol, 2006 Mar, 78: 245−253.
6. Clemons M, Dranitsaris G, Cole D, *et al.* Too much, too little, too late to start again? Assessing the efficacy of bisphosphonates in patients with bone metastases from breast cancer. Oncologist, 2006 Mar, 11: 227−233.
7. Carteni G, Bordonaro R,Giotta F, *et al.* Efficacy and safety of zoledronic acid in patients with breast cancer metastatic to bone: a multicenter clinical trial. Oncologist, 2006 Jul−Aug, 11: 841−848.

8. Ubieto MA, Abos MD, Tardin AL, *et al.* Treatment of bone metastatic pain with Sm153−EDTMP. Evaluation of the analgesic response and the existence of differences according to the primary tumor and the metastatic pattern. Rev Esp Med Nucl, 2005 Sep−Oct,24: 297−304.

9. Tripathi M, Singhal T, Chandrasekhar N, *et al.* Samarium−153 ethylenediamine tetramethylene phosphonate therapy for bone pain palliation in skeletal metastases. Indian J Cancer, 2006 Apr−Jun, 43: 86−92.

10. Damerla V, Packianathan S, Boerner PS, *et al.* Recent developments in nuclear medicine in the management of bone metastases: a review and perspective. Am J Clin Oncol, 2005 Oct, 28: 513−520.

11.Ogawa K, Mukai T, Asano D, *et al.* Therapeutic Effects of a 186Re−Complex−Conjugated Bisphosphonate for the Palliation of Metastatic Bone Pain in an Animal Model. J Nucl Med, 2007 Jan, 48: 122−127.

12. Storto G, Klain M, Paone G, *et al.* Combined therapy of Sr−89 and zoledronic acid in patients with painful bone metastases. Bone, 2006 Jul ,39: 35−41.

13. Vassiliou V, Kalogeropoulou C, Christopoulos C, *et al.* Combination ibandronate and radiotherapy for the treatment of bone metastases: Clinical evaluation and radiologic assessment. Int J Radiat Oncol Biol Phys, 2007 Jan 1, 67: 264−272.

14. Pons F, Fuster D, Vidal−Sicart S. Palliative treatment of metastasic bone pain. Rev Esp Med Nucl, 2003 Nov, 22: 429−438.