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Newer Techniques for Bone Pain Palliation in Patients with Skeletal Metastasis

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Introduction

Advanced cancer often metastasizes to the bone, causing significant discomfort, pain, impaired daily activity and reduced quality of life. Cancer incidence is on a rising trend in this day and era. And a big proportion of cancer patients have bony metastasis, which causes severe pain, which in majority of cases is even resistant to opioids and high grade analgesics. Currently available treatment options include analgesics, bisphosphonates, chemotherapy, radiation, surgery, hormone therapy, but come with the disadvantage of reduced efficacy and a wide spectrum of side effects. In this review, we try to discuss and summarize newer therapies like alpha radionuclide therapy, image-guided energy ablation, FLASH radiotherapy, and intrathecal drug delivery systems show promise in improving pain management and quality of life for these patients.

Discussion

Bone metastases often occur in cancer and are associated with severe pain from cancer. Lung and breast cancer account for 70% of bone metastases in India. Additionally, 85% people who develop or die from metastasis have lung, breast, or lung cancer. Less common types of bone metastases include prostate cancer, melanoma, and colon cancer. Bone metastases are the third most common metastases after lung and liver metastases and are common in cancer patients. It is estimated that 40% to 70% of patients with primary breast, prostate, and lung cancer will develop bone metastases at some point in their lives. The median overall survival for patients with breast cancer and prostate bone metastases is generally between two to four years, while the median overall survival for lung cancer patients is more than six months. These tumors are generally classified as mixed, osteolytic, or osteoblastic metastases. The biggest problem with of bone metastases is bone pain, which shortens life expectancy. It is difficult to improve patients' quality of life while they are still alive. Diagnosis of bone metastases can be done using a variety of methods, including hybrid SPECT/CT and PET/CT imaging, planar radiography, computed tomography (CT), magnetic resonance imaging (MRI), and single photon emission tomography (SPECT) and tomography (positron tomography). Some of the more common currently used to treat metastatic bone disease include antibiotics, bisphosphonates, chemotherapy, External Beam Radiation Therapy (EBRT), surgery, hormonal but come with reduced efficacy and a lot of side effects. The use of radionuclides is another way to treat bone cancer and has many advantages, including the ability to treat multiple metastatic tumors simultaneously, the ability to regenerate, and the ability to be used in conjunction with other treatments [1].

The currently available information provides a variety of treatments for pain caused by bone metastases, including radiation therapy, opioids, bisphosphonates, non-steroidal anti-inflammatory drugs, and surgical resection. Although patient response rates to traditional treatments such as radiation therapy have been reported to be as high as 72%–75%, most studies of patients receiving this treatment have shown a response rate of 45.4%. The combination of disease and current treatment limitations necessitates new evidence-based strategies in this field of research [2].

Radionuclide-targeted therapy not only reduces or delays the occurrence of Skeletal Events (SREs) and such serious complications but also provides anesthesia. These tracers may act as calcium transfer agents or bind to hydroxyapatite in bone releasing ionizing radiation in areas of the body with increased osteoblast activity. Most studies based on radiopharmaceuticals have shown to have positive results. Studies have shown that patients with osteoblastic disease are better treated.

Finally, new treatments are being used, such as imageguided energy ablation therapy, flash radiation, advanced palliative radiation therapy protocols, intrathecal drug delivery systems, arterial embolization, and recently developed alpha emission radionuclides such as 223Ra, 143Pr. They have good clinical value in preclinical research and clinical practice.

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[223Ra] Radium dichloride is an alpha emitter. Alpha emitters deliver more radiation to the tumor and less radiation to surrounding cells. [223Ra]Ra has been shown to be less toxic in hematology because it is shorter in tissue than beta emitters. With mild and reversible myelosuppressive therapy, remission occurs after a few weeks from nadir (e.g., 24 weeks after i.v. injections). Nausea, diarrhea, and vomiting also occur in 10% of patients. According to the results of two studies, current agreement will may help 40% to 71% and 29% to 75% of patients with osteoporosis, respectively. Combination with conventional therapy may improve survival. It is not surprising that trials of [223Ra]RaCl are ongoing against many cancers, including breast, colon, and breast cancer. In phase II trials, [223Ra]RaCl was used in combination with various hormonal agents. Disease control at nine months was the ultimate endpoint, achieved in 49% of patients. Studies are also ongoing to evaluate the efficacy of [223Ra]RaCl in combination with hormonal therapy and capecitabine therapy [3,4].

During palliative arterial embolization using N-butyl cyanoacrylate Lipiodal, more than 90% of arteries with a nutritional deficiency are bypassed. The mean duration of pain relief was 9.5 months (range: 8 to 12 months, $p<0.05$), with a 50% reduction in analgesic requirements. At 12-month follow-up, the mean size of the metastatic tumor was 67.9 cm^3 (range, 38.5 to 86.1 cm^3), compared with 71.5 cm^3 (range, 41.6 to 90.3 cm^3) before embolization. Therefore, it is considered a safe and effective palliative treatment for patients improve after radiotherapy, thus providing an effective treatment for cancer patients with mild to severe disease. It can achieve pain management for cancer patients with moderate to severe pain. Intrathecal administration can provide a complete recovery in cancer patients. This is supported by several randomized clinical trials showing that the addition of implantable intrathecal devices to routine care improves outcomes in patients with breast cancer.

The intrathecal pump is a new treatment modality for patients with metastatic bone disease resistant to conventional therapy and can reduce side effects by 50%. It can achieve complete pain recovery in cancer patients. This is supported by several clinical studies showing that the addition of intrathecal implants to routine care improves outcomes for cancer patients. Continuous infusion is delivered by a pump implanted in the subcutaneous fat of the abdomen. The most commonly used pumps today are programmable, with electronic devices that can be operated via telemetry to vary the infusion. Very high doses of at least 40 Gy/s can be delivered [6,7].

Compared to traditional radiation therapy, FLASH radiation therapy is a newer modality, and one mechanism by which FLASH is thought to benefit tissue is that FLASH reduces the level of oxygen reactive species in tissue compared with conventional RT. After three months, 66.7% of patients had a complete response to FLASH treatment. During the follow-up period, 16.73% (2 out of 12) of FLASH clinics required additional care. This treatment was also well received and tolerated by all patients [7].

When treating large tumors, GRID therapy (also known as spatially fractionated radiotherapy) can also be used to provide a dose escalation approach that improves local control while reducing toxicity. Combining or following radiotherapy with ablative techniques such as thermal ablation or cryoablation may also improve the treatment of bone metastases.

Pain relief can also be achieved by another newer modality-energy guided ablation, but the frequency of postprocedure side effects varies. Future critical studies are needed with main focus on using evidence based, qualitative, consistent and comparative data to improve future research.

In the past few years, minimally invasive or noninvasive image-guided percutaneous thermal ablation, such as radiofrequency ablation, has become the treatment of choice for patients with initially incurable or painful bone [5]. Advantages include immediate visualization of the ablation images, modification of the size and shape of the ablation area according to the target lesion, reducing pain and postoperative pain, and reduction of the postoperative pain burden in the hospital or microwave ablation. Pain scores decreased by 62.5%, 70%, and 80.9% at 24 h, 3 months, and 6 months after cryoablation, respectively. Cryoablation can rapidly and permanently reduce metastatic bone pain levels while improving quality of life in patients do not respond to or are not suitable for conventional treatments [6].

Thermal ablation technology image (MRI)-guided focused ultrasound (MRgFUS) allows physicians to use acoustic power to locally remove the desired amount of tumor volume and is a new treatment strategy being introduced among metastatic bone disease therapy options. MR guidance allows for instantaneous monitoring of the location and temperature of the treatment area. The use of MRgFUS to treat bone tissue has several advantages over Soft Tissue Therapy (STT), including the thermal conductivity of bone and its ability to absorb upto 50 times more acoustic energy than STTs. Access to normal cortical bone is limited. Since MRgFUS uses noninvasive, nonionizing, precise ablation, the side effects as seen in other treatment options usually are not seen. In the clinical setting, local bone denervation caused by heat induced degeneration of the periosteal layer in the treatment area can cause sudden pain. Since acoustic energy is non-ionizing, there is no upper limit to the amount of energy that can pass through adjacent tissue as long as tissue temperature is adequately controlled. At the 3-month followup, 72% (18/25) of patients at highest dose reported significant pain (>2 points). 52% of patients reported severe pain three days after starting treatment [14].

An investigational new radiopharmaceutical called Sn-117m-DTPA is being considered for the treatment of bone metastases. Low abundance γ photons (159 keV) and low energy transition electrons (Emax 0.16 MeV) are released during decay. Its physical half-life is 13.6 days. Best blood and tissue clearance is achieved by chelation with Diethylenetriaminepentaacetic Acid (DTPA). The rarity of myelosuppression may be due to the small volume of only 0.3 mm of the large force transmitted by the tissue. It has no affinity for hydroxyapatite. Two proposed local pathways are interaction with hydroxyapatite or formation of tin oxide on bone. Treatment and healing have been successful in 30% patients receiving this therapy [10]. In addition to the poor dose relationship, these drugs begin to reduce pain earlier than other drugs. Treatment with a dose of 444 MBq (12 mCi) (per 70 kg body weight) was observed in just one week.

Conclusion

Bone metastasis in cases of advanced cancer often results in severe pain and pathological bone diseases. Use of conventional therapies are all limited due to lower efficacy and side effects. New treatments such as intrathecal drug use, FLASH irradiation, image-guided energy ablation, alpha radionuclide therapy along with other newer tracers, GRID therapy can improve patients' quality of life and pain management without serious side effects. New radionuclide

techniques, especially future alpha emitter, is changing, and many future radionuclide tracers are currently in the preclinical stage. These tracers are better at treating Metastatic disease and are better at reducing pain from a variety of bone metastases with fewer side effects compared to other currently available treatments.

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