Chapter 28

BONE METASTASIS, SKELETAL RELATED EVENTS AND TREATMENT APPROACH

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INTRODUCTION

Skeletal-related events (SREs) developing in association with bone metastases in metastatic cancer patients are conditions exerting a negative impact on quality of life. Pathological fractures, spinal cord compression and conditions requiring radiotherapy or surgical intervention to bone are defined as SREs [1]. Bone metastasis occurs most commonly in breast, prostate and lung cancers [2]. With recent developments in targeted treatments and immunotherapy, longer survival has been obtained in metastatic diseases [3]. In association with this development, morbidities related to bone metastasis have also increased. Early diagnosis and prophylactic treatment have an important place in metastatic patients in order to prevent serious SREs, due to their positive contribution to quality of life and general survival. SREs treatment should be organized in a multidisciplinary manner with the participation of specialists from medical oncology, radiation oncology, nuclear medicine, and orthopedics departments [4]. In this chapter, the use of especialy biphosphonate, which is used commonly in SREs treatment and denosumab, which has recently been started to be used more commonly, was adressed.

EPIDEMIOLOGY

The organ in which distant metastasis occurs most frequently after liver and lung is the bone [2]. Autopsy studies have demonstrated that 70-90% of patients with breast and prostate cancer have bone metastasis [5]. Among solid organ tumors, breast, prostate, lung, thyroid and renal cancers account for 80% of patients with bone metastases. The remaining ones are malignant melanoma, sarcomas, gastrointestinal tumors and uterine carcinomas [6]. Bone metastases occur most commonly in lumbar vertebrae, to be followed by thoracal vertebrae, cervical vertebrae and sacrum [4].

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In a phase III study, carried out with patients with metastastic breast cancers, it was demonstrated that the use of Zoledronic acid every 12 weeks is not different from its use every 4 weeks in terms of preventing SRE [25]. Zoledronic acid administered at 4 mg dose IV in 15 minutes for two years every 4 weeks or every 12 weeks. Owing to the risk of renal toxicity, kidney functions tests should be performed periodicallly. Mandibular osteonecrosis, associated with IV biphosphonates, occur at the rate of about 5% [24].

Denosumab

Denosumab is an human monoclonal antibody developed against RANKL, which is an important regulator of osteoclast mediated bone resorbtion. It was compared with Zoledronic acid, in similarly designed 3 randomized Phase III clinical studies. Patients with breast cancer, prostate cancer with bone metastasis and multiple myeloma were included in the studies. In these studies, it was demonstrated that Denosumab is superior to Zoledronic acid in terms of time to occurence of first SRE [26-28]. Although side effects were similar in both groups, grade 3-4 hypocalcemia occurred at a higher rate (%3,7) in denosumab group, than that ocurring in Zoledronic acid group (%1,7). In Zoledronic acid arm, acute phase reaction (%20,2 vs %8,7) and renal toxicity (%11,8 vs 9,2) occurred at a higher rate than denosumab arm [27, 28]. Denosumab should be used in conjunction with oral calcium and Vitamin D. It is used 120mg subcutaneously every four weeks for two years. Unlike Zoledronic acid, it can be safely used in patients with renal failure.

REFERENCES

1. Stopeck, A.T., et al., Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. Support Care Cancer, 2016. 24(1): p. 447-55.
2. Mundy, G.R., Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer, 2002. 2(8): p. 584-93.
3. Michiels, S., E.D. Saad, and M. Buyse, Progression-Free Survival as a Surrogate for Overall Survival in Clinical Trials of Targeted Therapy in Advanced Solid Tumors. Drugs, 2017. 77(7): p. 713-719.
4. Kimura, T., Multidisciplinary Approach for Bone Metastasis: A Review. Cancers (Basel), 2018. 10(6).
5. Bubendorf, L., et al., Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol, 2000. 31(5): p. 578-83.
6. Tubiana-Hulin, M., Incidence, prevalence and distribution of bone metastases. Bone, 1991. 12 Suppl 1: p. S9-10.
7. Ibrahim, T., et al., Multidisciplinary approach to the treatment of bone metastases: Osteo-Oncology Center, a new organizational model. Tumori, 2009. 95(3): p. 291-7.
8. Marino, S. and G.D. Roodman, Multiple Myeloma and Bone: The Fatal Interaction. Cold Spring Harb Perspect Med, 2018. 8(8).

9. Yang, Y.H., et al., Semaphorin 4D Promotes Skeletal Metastasis in Breast Cancer. PLoS One, 2016. 11(2): p. e0150151.
10. Fornetti, J., A.L. Welm, and S.A. Stewart, Understanding the Bone in Cancer Metastasis. J Bone Miner Res, 2018. 33(12): p. 2099-2113.
11. Weilbaecher, K.N., T.A. Guise, and L.K. McCauley, Cancer to bone: a fatal attraction. Nat Rev Cancer, 2011. 11(6): p. 411-25.
12. Howard, L.E., et al., Do skeletal-related events predict overall survival in men with metastatic castration-resistant prostate cancer? Prostate Cancer Prostatic Dis, 2016. 19(4): p. 380-384.
13. Rades, D. and J.L. Abrahm, The role of radiotherapy for metastatic epidural spinal cord compression. Nat Rev Clin Oncol, 2010. 7(10): p. 590-8.
14. Bryson, D.J., L. Wicks, and R.U. Ashford, The investigation and management of suspected malignant pathological fractures: a review for the general orthopaedic surgeon. Injury, 2015. 46(10): p. 1891-9.
15. Goldner, W., Cancer-Related Hypercalcemia. J Oncol Pract, 2016. 12(5): p. 426-32.
16. Huysse, W., et al., Prospective Comparison of F-18 Choline PET/CT Scan Versus Axial MRI for Detecting Bone Metastasis in Biochemically Relapsed Prostate Cancer Patients. Diagnostics (Basel), 2017. 7(4).
17. Langsteger, W., et al., (18)F-NaF-PET/CT and (99m)Tc-MDP Bone Scintigraphy in the Detection of Bone Metastases in Prostate Cancer. Semin Nucl Med, 2016. 46(6): p. 491-501.
18. Zhu, X.C., et al., Advances in cancer pain from bone metastasis. Drug Des Devel Ther, 2015. 9: p. 4239-45.
19. Westhoff, P.G., et al., Course of Quality of Life After Radiation Therapy for Painful Bone Metastases: A Detailed Analysis From the Dutch Bone Metastasis Study. Int J Radiat Oncol Biol Phys, 2016. 95(5): p. 1391-1398.
20. Choi, J.Y., Treatment of Bone Metastasis with Bone-Targeting Radiopharmaceuticals. Nucl Med Mol Imaging, 2018. 52(3): p. 200-207.
21. Skovlund Sorensen, M., et al., Incidence of surgical interventions for metastatic bone disease in the extremities: a population-based cohort study. Acta Oncol, 2019: p. 1-7.
22. Sutcliffe, P., et al., A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. Health Technol Assess, 2013. 17(42): p. 1-274.
23. Hillner, B.E., et al., American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol, 2003. 21(21): p. 4042-57.
24. Woo, S.B., J.W. Hellstein, and J.R. Kalmar, Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med, 2006. 144(10): p. 753-61.
25. Hortobagyi, G.N., et al., Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol, 2017. 3(7): p. 906-912.
26. Stopeck, A.T., et al., Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol, 2010. 28(35): p. 5132-9.
27. Fizazi, K., et al., Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet, 2011. 377(9768): p. 813-22.
28. Henry, D.H., et al., Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol, 2011. 29(9): p. 1125-32.