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REVIEW

Systemic Treatments in Bone Metastatic Disease: NSCLC and Other Solid Tumors

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Introduction

Treatment approach of bone metastatic disease needs multidisciplinary approach that use radiotherapy, surgery, medical therapy with chemotherapy, immunotherapy, targeted treatments, analgesics and bone resorption inhibitors. Treatment should also be tailored according to histopathology, comorbidities and performancestatus.

Nonsmall cell lung cancer (NSCLC)

NSCLC often metastasizes to bone at the frequency of 30-65% and causes pain, skeletal-related events (SRE) with physical inactivity, and disability which negatively impacts cancer outcomes and survival with a median of 6 months.[1,2] The mean skeletal morbidity rate (annual SREs) among patients with bone metastatic disease (BMD) from lung cancer and other solid tumors is 2.71.[1] BMD disturbs the balance between osteoblastic bone formation and osteoclastic bone resorption, finally resulting in a loss of the normal structural integrity of the skeleton. BMD for lung cancer is grouped into three categories: osteoblastic (30%), osteoclastic (40%), and mixed metastases (10%).[3] Solitary lesions and oligo-metastases can be treated using curative intent, as mentioned before. Treatment options for diffuse involvement are opiate analgesics, bone resorption inhibitors (BRI), local radiotherapy, and radionuclide therapy.[2]

Recent reports showed a reduction in SREs and bone pain with the use of bisphosphonates and anti-receptor activator of nuclear factor kappa-B ligand (RANKL) monoclonal antibody (denosumab) for BMD of lung cancer.[1,3,4] Meta-analysis of 12 trials reported a 19% reduction in SRE risk (relative risk 0.81, 95% confidence interval [CI] 0.67-0.97), delay in time to first SRE (mean differences [MD] 163 days; 95% CI 45.2-278.8), and 72-day survival improvement trend (95% CI 8.9-152.9, p=0.08) using bisphosphonates. Bisphosphonate combined with radiation showed the best pain control while monotherapy was not superior to chemotherapy, radiation therapy, or radioisotope therapy on behalf of pain control in lung cancer BMD.[3] Denosumab was non-inferior to zoledronic acid (ZA) in delaying time to first SRE[4]; however, was superior in improvement of overall survival (1.5 months) compared with ZA (median overall survival [mOS] 9.5 months vs. 8.0 months; hazard ratio =0.78; 95% CI=0.65-0.94; p=0.01).[5] It is recommended to start bisphosphonates or denosumab as soon as bone metastases are diagnosed to delay the first SRE and reduce skeletal morbidity from BMD.[1-5]

Conventional cytotoxic chemotherapy, antiangiogenic agents, or immune checkpoint inhibitors (ICI) have not shown a significant advantage in bone homing or inhibiting the behavior of bone metastasis in lung cancer.[2,6,7] CheckMate 057 and CheckMate 227 also supported lower sensitivity to immunotherapy and poor prognosis in bone metastatic non-small cell lung cancer (NSCLC).[8,9]

RANK/RANKL interplays between the bone and immune system, making osteoclasts' function as antigen-presenting cells; therefore, they assist in osteoimmune regulation by activating CD4+ and CD8+ T cells. This system also induces chemoresistance through the activation of multiple signal transduction pathways. Hereby, with the addition of a RANKL-mAb to chemo-

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therapy or ICI mAbs, T-cell effector function and tumor cytotoxic T-lymphocyte infiltration are increased, leading to increased anti-tumor activity in lung cancer.[5,10,11] Retrospective real-world data of 241 patients with metastatic NSCLC (31% of patients with metastatic disease limited to the bone) treated using ICI mAbs, and denosumab showed better survival and a better response rate (objective response rate [ORR] of 33% and disease control rate of 58%) in favor of the combination of ICI and BRI, without an increase in toxicities.[12]

Targeted therapies have improved the skeletal outcomes of patients with osteotropic cancers by modulating the bone microenvironment and immune response; however, their effects on bone remodeling differ depending on the molecules, duration, and doses used.[10,12] Endothelial growth factor receptor (EGFR) mutated patients with NSCLC have earlier onset and a higher rate of bone metastases.[6,13] A retrospective study[6] of NSCLC reported fewer SREs with gefitinib/erlotinib EGFR tyrosine kinase inhibitor (TKI) (the incidence rate of 4.4% per cycle) compared to cytotoxic chemotherapy (7.3% per cycle; p=0.004).

There is also preclinical evidence of bisphosphonates that has intrinsic antitumoral effect by inducing apoptosis and inhibiting cell growth in NCSLC cell lines, and also increases the effectiveness of chemotherapeutics such as paclitaxel, etoposide, cisplatin, and gemcitabine.[14]

Other Solid Tumors

Thyroid cancers (from 13% to 60% incidence of bone metastases), renal cell cancers (30% incidence), bladder cancer (40% incidence), and melanoma (15-45% incidence) are other solid tumors in which BMD are most frequently observed.[1,15,16] Systemic anti-tumor treatment for BMD is selected due to the pathological type of the tumor. Local palliative treatments (stereotactic body radiation therapy, radiofrequency, and cement injection) and BRIs reduced the SRE and bone pain.[1,4,15-18]

Thyroid differentiated follicular cancer presents more frequently with BMD than papillary subtype. Curative radioactive iodine therapy (RAI) is recommended for RAI avid bone lesions with a 55% efficacy rate.[17] Treatment cycles should be repeated until the clinical benefit is observed or on reaching high cumulative doses. Thyroid-stimulating hormone (TSH)-suppressive hormonal therapy with thyroxine must be given life-long due to the growth factor effect of TSH on differentiated thyroid cancers (DTC) and bone metastases. The Memorial Sloan-Kettering Cancer Center reported SRE rate was high (78%) for BMD of DTC.[18]Targeted therapies for RAI-refractory DTC have improved skeletal outcomes with sorafenib, sunitinib, and lenvatinib.[19,20]

The bone is the most common metastatic site in renal cell carcinoma (RCC) and SRE rate increases correlated with the increasing treatment line.[21] International Metastatic Renal Cell Carcinoma Database Consortium reported a retrospective analysis of more than 2000 patients with decreased OS and time to treatment failure (Median time to treatment failure of 5.7 vs. 7.6 months; p<0.0001) with BMD when compared to patients without bone involvement (mOS of 14.9 vs. 25.1 months; p<0.0001).[22] TKIs have improved the skeletal outcomes of BMD by the inhibition of c-mesenchymal epithelial transition (MET) and vascular endothelial growth factor receptors (VEGFR) in osteoblasts which reduces the expression of RANKL and monocyte colony-stimulating factor (M-CSF) and is associated with decreased tumor-induced osteolysis.[23]

Retrospective data reported that bisphosphonate therapy concomitant with VEGF-targeted therapy may improve survival in patients with bone metastatic RCC; however, it may be associated with an increased risk of jaw osteonecrosis.[22] Cabozantinib, a TKI that acts against VEGFR2, AXL, and MET, reduces the serum total alkaline phosphatase and C-terminal telopeptide of type I collagen levels by ≥50% in BMD[24]. mTOR is an anti-apoptotic target acting downstream of M-CSF, RANKL, and tumor necrosis factor-α, which is essential for the differentiation, survival, and activity of osteoclasts. Impairment of the PI3K/AKT/mTOR pathway is involved in carcinogenic osteoclast genesis. Treatment using ZA concomitant with mTOR inhibition show additive effects on antiresorptive and anti-tumor function.[23]

Melanoma often metastasizes to bone and is treated using the same local treatment procedures and BRIs. Retrospective real-world data of 66 patients with metastatic malign melanoma (9% of patients had metastatic disease limited to the bone) treated using concomitant ICI mAbs and denosumab showed a better response rate (ORR of 41%) in favor of the combination of ICI and BRI, without an increase in toxicities.[12]

Ongoing clinical trials are addressing the combination of ICI and denosumab in stage IV NSCLC with bone metastases-DENIVOS study- (NCT03669523); clear cell metastatic renal cancer-KEYPAD study-(NCT03280667), and unresectable or metastatic malign melanoma-CHARLI study- (NCT03161756).

References

1. Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krzakowski M, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with non-small cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Cancer 2004;100(12):2613–21.
2. Decroisette C, Monnet I, Berard H, Quere G, Le Caer H, Bota S, et al. Epidemiology and treatment costs of bone metastases from lung cancer: a French prospective, observational, multicenter study (GFPC 0601). J Thorac Oncol 2011;6(3):576–82.
3. Lopez-Olivo MA, Shah NA, Pratt G, Risser JM, Symanski E, Suarez-Almazor ME. Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. Support Care Cancer 2012;20(11):2985–98.
4. Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, 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):1125–32.
5. Scagliotti GV, Hirsh V, Siena S, Henry DH, Woll PJ, Manegold C, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. JThorac Oncol 2012;7(12):1823–29.
6. Sun JM, Ahn JS, Lee S, Kim JA, Lee J, Park YH, et al. Predictors of skeletal-related events in non-small cell lung cancer patients with bone metastases. Lung Cancer2011;71(1):89–93.
7. Landi L, D'Incà F, Gelibter A, Chiari R, Grossi F, Delmonte A, et al. Bone metastases and immunotherapy in patients with advanced non-small-cell lung cancer. J Immunother Cancer 2019;7(1):316.
8. Peters S, Cappuzzo F, Horn L, Paz-Ares L, Borghaei H, Barlesi F, et al. OA03. 05 Analysis of early survival in patients with advanced non-squamous NSCLC treated with nivolumab vs docetaxel in CheckMate 057. J Thorac Oncol 2017;12(1):S253.
9. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med 2019;381(21):2020–31.
10. Turpin A, Duterque-Coquillaud M, Vieillard MH. Bone metastasis: current state of play. Transl Oncol 2020;13(2):308–20.
11. van Dam PA, Verhoeven Y, Trinh XB, Wouters A, Lardon F, Prenen H, et al. RANK/RANKL signaling inhibition may improve the effectiveness of checkpoint blockade in cancer treatment. Crit Rev Oncol Hematol 2019;133:85–91.
12. Liede A, Hernandez RK, Wade SW, Bo R, Nussbaum NC, Ahern E, et al. An observational study of concomitant immunotherapies and denosumab in patients with advanced melanoma or lung cancer. Oncoimmunology 2018;7(12):e1480301.
13. Laganà M, Gurizzan C, Roca E, Cortinovis D, Signorelli D, Pagani F, et al. High prevalence and early occurrence of skeletal complications in EGFR mutated NSCLC patients with bone metastases. Front Oncol 2020;10:588862.
14. Decoster L, de Marinis F, Syrigos K, Hirsh V, Nackaerts K. Bisphosphonates: prevention of bone metastases in lung cancer. Recent Results Cancer Res 2012;192:93–108.
15. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27(3):165–76.
16. Grávalos C, Rodríguez C, Sabino A, Seguí MÁ, Virizuela JA, Carmona A, et al. SEOM Clinical Guideline for bone metastases from solid tumours (2016). Clin Transl Oncol2016;18(12):1243–53.
17. Andrade F, Probstner D, Decnop M, Bulzico D, Momesso D, et al. The impact of zoledronic acid and radioactive iodine therapy on morbi-mortality of patients with bone metastases of thyroid cancer derived from follicular cells. Eur Thyroid J 2019;8(1):46–55.
18. Farooki A, Leung V, Tala H, Tuttle RM. Skeletal-related events due to bone metastases from differentiated thyroid cancer. J Clin Endocrinol Metab 2012;97(7):2433–9.
19. Matta-Coelho C, Simões-Pereira J, Vilar H, Leite V. Bone metastases from thyroid carcinoma of follicular origin: a single institutional experience. Eur Thyroid J 2019;8(2):96–101.
20. Trigo JM, Capdevila J, Grande E, Grau J, Lianes P; Spanish Society for Medical Oncology. Thyroid cancer: SEOM clinical guidelines. Clin Transl Oncol 2014;16(12):1035–42.
21. Bianchi M, Sun M, Jeldres C, Shariat SF, Trinh Q-D, Briganti A, et al. Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol 2012;23(4):973–80.
22. McKay RR, Kroeger N, Xie W, Lee JL, Knox JJ, Bjarnason GA, et al. Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. Eur Urol 2014;65(3):577–84.
23. Turpin A, Duterque-Coquillaud M, Vieillard MH. Bone metastasis: current state of play. Transl Oncol 2020;13(2):308–20.
24. Abdelaziz A, Vaishampayan U. Cabozantinib for the treatment of kidney cancer. Expert Rev Anticancer Ther 2017;17(7):577–84.