

Advances in treatment of metastatic breast cancer with bone metastasis

Ziping Wu, Jinsong Lu

Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

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Correspondence to: Jinsong Lu. Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, No.160 Pujian Road, Shanghai 200127, China. Email: lujss@163.com.

Abstract: Bone is the most commonly seen metastatic site in all the metastatic breast cancer (MBC). Treatment includes systemic treatment according to different molecular subtypes and specified treatment of the bone. Bisphosphonate and denosumab are the only two drugs approved to use in bone metastatic site. The optimal dosing schedule and duration of the drugs are still under research. New drugs and therapies including curcuminoids, sunitinib and nano particles are potentially available in the near future.

Keywords: Metastatic breast cancer (MBC); bone metastasis (BM); bisphosphonate; denosumab

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Introduction

Clinically, the incidence of bone metastasis (BM) count for 60–70% of all the metastatic breast cancer (MBC) (1–3). Common complications of BM include pathological fracture, spinal compression, hypercalcemia and persistent pain. One important concept of BM treatment is called skeletal-related events (SREs), which are defined as: a pathologic fracture, a spinal cord compression, a necessity for radiation to bone (for pain or impending fracture) or surgery to bone (4). Once an SRE is developed, the 5-year survival rate of MBC patients drops from 8.3% for patients with bone metastases to 2.5% for those with both bone metastases and SREs (5). Thus, one major goal of BM management is to prevent SREs.

Treatments include systemic treatment and specified therapy for bone.

Systemic treatment

Around 60–70% of the BM patients were hormone receptor positive and HER2 negative (3,6,7). If the patient

presents with a luminal breast cancer with BM only, then sole endocrine therapy is reasonable for the start (8). If the patient is presented with other tumor subtypes or luminal subtype with visceral crisis, then chemotherapy is urgently needed.

One interesting issue is that do we concern the operation of the primary tumor in *de novo* MBC with BM? One randomized clinical trial (RCT) from Turkish directly compares loco-regional surgery (LRS) of the primary tumor site followed by appropriate systemic therapy (ST) versus ST alone in treatment naive stage IV BC patients. It turned out that overall survival (OS) was similar between the two groups. However, in unplanned subgroup analyses, OS was statistically higher in LRS group than ST group: ER/PR (+) (HR =0.64, 95% CI: 0.46–0.91, P=0.01), HER2 (-) (HR =0.64, 95% CI: 0.45–0.91; P=0.01), patients <55 years (HR =0.57, 95% CI: 0.38–0.86; P=0.006), and solitary bone only metastasis (HR =0.47, 95% CI: 0.23–0.98; P=0.04) (9).

Thus, in the latest European Society for Medical Oncology (ESMO) consensus, 70.4% of the panel agreed with the idea that “*the removal of the primary tumor in patients with de novo stage IV breast cancer has not been associated with*

prolongation of survival, with the possible exception of the subset of patients with bone only disease.” (8).

Loco-regional treatment of the bone

Surgery of the bone/radiotherapy (RT)

If a fracture of the bone has occurred or is likely to occur, then an orthopedic assessment is necessary to determine if a surgical intervention is needed before RT or RT alone is adequate. In emergent cases where a spinal compression has occurred, surgical decompression is the optimal treatment of choice. If surgery is not feasible, then an emergent RT is also an option (8,10).

Bone modifier

Bisphosphonates and denosumab are two targeted drugs approved in MBC patients with BM. To date, no study of either drug has demonstrated an impact on OS in patients with metastatic disease. However, they could reduce the risk of SREs and improve the quality of life of the patients (10).

Bisphosphonates

Bisphosphonates target osteoclast farnesyl pyrophosphate synthase (FPPS) and inhibit protein prenylation, thus prevent SREs by inhibiting osteoclast-mediated bone resorption (11). A Cochrane analysis showed that bisphosphonates could reduce the risk of SREs by 14% in MBC patients with BM compared with placebo/no bisphosphonates, and delay the median time to an SRE and reduce bone pain (2). Either oral or intravenous administration exhibits this persistent benefit. Intravenously pamidronate and zoledronic acid are approved in United States, while oral ibandronate and clodronate are approved in European countries.

Though one RCT comparing intravenous zoledronic acid at 4 mg every 3–4 weeks or oral ibandronic acid revealed a lower SREs rate in zoledronic acid group (43.5% vs. 49.9%, RR =1.148, 95% CI: 0.967–1.362). The oral ibandronic acid group showed lower renal toxicity (12), which might also be an option for patients with impaired renal function.

The optimal duration of bisphosphonate administration is under discussion and investigation due to safety and economic concerns of prolonged usage. Currently more and more evidence suggest that a 12-week schedule could replace the original 4-week schedule after a period of initial

use (around 1 year) (13,14).

Two RCTs directly compared 12-week schedule zoledronic acid and 4-week zoledronic acid with non-inferior hypothesis. In OPTIMIZE-2, patients with bone metastases from breast cancer who had previously received 10 to 15 months of bisphosphonate therapy were randomly assigned to receive sequential 4-week or 12-week zoledronic acid. The SREs rate was 22.0% in the 4-week group and 23.2% in the 12-week group (noninferiority P=0.02) showing a non-inferior efficacy (13). In ZOOM trial, which was similarly designed as OPTIMIZE-2, the skeletal morbidity rate was 26% in the 12-week group and 22% in the 4-week group (15). In this trial “*The between-group difference was 0.04 and the upper limit of the one tailed 97.5% CI was 0.17*”, indicating that the 12-week schedule was non-inferior to the 4-week schedule. However, when considering cost-effective (CE) issue, initial 12-week zoledronic acid is the more CE option and more reasonable alternative to 4-week zoledronic acid (16).

The latest recommendations from the National Comprehensive Cancer Network (NCCN) and ESMO are still to start with the 4-week schedule for the first year and then switch to a 12-week schedule. The overall duration of bisphosphonate are still not clear yet, but long-term toxicity should be taken in to account in clinical practice.

Denosumab

Denosumab is a fully human monoclonal antibody that inhibits osteoclasts by binding to the receptor activator of nuclear factor kappa B ligand (RANK) (17). In an RCT, denosumab delays the onset of the first and subsequent SREs compared to zoledronic acid in MBC patients with BM (18). Based on this evidence, NCCN guideline recommends that women who were candidate of bisphosphonate might also consider denosumab for the treatment (10).

In a Cochrane analysis that involved 44 RCTs, denosumab reduced the risk of SREs by 22% compared with bisphosphonates (2). The rate of adverse events and severe adverse events are similar between these two drugs.

New drugs

A great amount of new drugs targeting bone metastatic sites are under development and going through clinical trials.

Curcuminoids is a class of phenols isolated from the dried rhizomes of turmeric. A study from Wright *et al.* showed that curcuminoids prevent TGF- β induction of

PTHrP and reduce osteolytic bone destruction by blockade of Smad signaling in breast cancer cells (19).

Schroeder *et al.* evaluated the effect of angiogenesis inhibitor sunitinib in an *in vivo* model of MBC with BM, and showed that sunitinib could also reduce tumor growth and limit changes in microvascular properties in breast cancer growth in bone (20).

Another new strategy is to combine chemo-regimen with antigen-specified nano particles to maximally reduce adverse events. For example, integrin $\beta 3$ ($\beta 3$) was strongly expressed on bone metastatic cancer cells, but not primary tumors or other metastatic sites. Micelle-based nanoparticle therapy with $\alpha\beta 3$ -MP-docetaxel, which recognizes integrin $\alpha\beta 3$ in breast cancer cells in the bone, showed great anti-tumor activity with less bone destruction and less hepatotoxicity compared with equal doses of free docetaxel (21).

Conclusions

BM is the most common metastasis in breast cancer. Current treatment strategies of the bone are surgeries, radiotherapies, bisphosphonates and denosumab. New interventions with more precise target on bone including small-molecular inhibitors and nano particles are very promising in the near future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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