State of art and advances on the treatment of bone metastases from breast cancer: a concise review

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Abstract: Bone is one of the most common metastatic sites in metastatic breast cancer (mBC). The presence of bone metastases can lead to various complications including pain, spinal cord compression, hypercalcaemia, pathological fractures. The treatment of bone metastases of breast cancer (BC) is mainly based on the biological characteristics of the primary tumour, but there are also specific treatments for bone lesions including bone modifiers, radionuclides, or localized treatments such as radiotherapy, surgery or vertebroplasty. In this review, we analyse the state of art of the common treatments and the advances of bone metastases of BC. Finally, we summarize the state of art of biomarkers in diagnosis, prognosis and prediction to therapy.

Keywords: Breast cancer (BC); bone metastases; bisphosphonates; denosumab; biomarkers

Introduction

Incidence of breast cancer (BC) is growing every year (1). Metastatic breast cancer (mBC) counts approximately 6–10% of new cases (2) ("de novo" metastatic disease), and it is estimated that 20% to 30% of all BC will develop metastases. Bone metastases (BM) count approximately 60–70% of all mBC (3,4) and more than 70% of patients showed bone metastases during autopsy (5). Among the most important complications of BM there are pain, pathological fractures, spinal compression and hypercalcemia.

This complex of events is often included in the definition of skeletal-related events (SREs), in which the need for radiotherapy or surgery for pain or spinal cord decompression is also considered. In mBC, SREs occur in about half to two thirds of patients with bone metastases (6). SREs remain a major cause of mortality and morbidity,

and has an impact on the quality of life (7). Furthermore, the occurrence of an SRE influences the median 5-year survival rate, reducing it from 8.3% to 2.5% (6). Therefore, reducing the risk of SRE is a priority objective in these patients, and it is recommended to administrate bone-modifying agents (BMAs) before symptomatic events (8-10). The purpose of this short review is to describe the state of the art of BM treatments, including systemic and loco-regional treatment of the bone. Finally, we will briefly discuss the current state of the art of promising biomarkers for the diagnosis and monitoring of BM.

Systemic treatments

Antitumor treatments

The choice of systemic therapy should be based on the biological characteristics of metastatic lesions. It would be

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preferable to obtain these biological characteristics from a biopsy of the metastatic lesions rather than infer them based on the characteristics of the primitive tumour, except for "de novo" mBC (11), due to the possible discrepancy in hormone receptor status and human epidermal receptor growth factor (HER2) status between primary BC and metastasis (12). Alongside systemic anticancer therapy, in presence of BM, there are several therapies focused on the treatment of bone lesions, such as bone modifiers or radionuclides.

Bone modifiers

Currently, in clinical practice bisphosphonates and denosumab are the two targeted-drugs most used in the treatment of BC BM.

Bisphosphonates act on the inhibition of protein prenylation by blocking the osteoclast farnesyl phyrophosphate synthase. The final effect is the inhibition of bone resorption (13).

The most common bisphosphonates in clinical practice for the treatment of BC BM are pamidronate and zoledronic acid.

In vitro, bisphosphonates shown to be able to inhibit tumour adhesion and neo-angiogenesis and to induce tumour apoptosis (14). *In vivo*, there are some evidences that bisphosphonates can reduce tumour burden also in extra-skeletal environment, such as liver and lung parenchyma, with a dose-dependent mechanism (15).

The action of bisphosphonates, and particularly of zoledronic acid, appears to be synergistic with doxorubicin chemotherapy. In fact, when zoledronic acid is administered 24 hours after doxorubicin, there is an up to 10-fold increase in tumour apoptosis. The most accredited hypothesis on these observations is a stronger uptake of zoledronic acid in chemotherapy-sensitized cells, leading to a greater tendency to arrest the cell cycle. These data has been recently confirmed by the ANZAC trial, a phase II trial that explored the activity of zoledronic acid given 24 hours after 5-fluorouracil-epirubicin-cyclophosphamide in neoadjuvant setting (16). Despite the interesting results shown in this trial, there were no important implications for dose scheduling in clinical practice on neoadjuvant setting.

Starting about 20 years ago, at least three trials evaluated the role of bisphosphonates in the BC adjuvant setting (17-19). The primary endpoints of these three trials were incidence of distant metastases (skeletal and non-skeletal), and overall survival (OS). The results were discordant and this discrepancy can be explained by heterogeneity of study population.

In the ABCSG-12 trial (20), 1,803 premenopausal patients with stage I/II luminal BC randomized to receive tamoxifen or anastrozole plus goserelin with or without zoledronic acid every 6 months (4 mg), for 3 years. The primary endpoints were disease-free survival (DFS) and recurrence-free survival (RFS). After a median follow-up of 4 years, there was an improvement in DFS of 36% in zoledronic acid arm (P=0.01) and a trend in favour of zoledronic acid on OS, but without statistical significance (HR 0.60, 95% CI: 0.32–1.11, P=0.11). Intriguingly, the benefit was not limited to skeletal events but it was also in terms of loco-regional and distant recurrence rates.

Two parallel trial, Z-FAST (21) and ZO-FAST (22), randomized a total of 2,195 postmenopausal patients with early BC to receive letrozole for 5 years and early (at start of study) or delayed (in case of T score ≤2.0 or osteoporotic fracture) zoledronic acid, respectively.

The primary endpoint was the change in lumbar spine bone density (BMD) at 12 months. Secondary endpoints were the change on lumbar spine and total hip BMD in the subsequent follow-up, DFS and OS. After 60 months of follow-up, there was a significant benefit in terms of BMD change on early zoledronic acid (+4.3% *vs.* –5.4%, P<0.0001). There was a benefit also in DFS in favour of early zolendronate group (relative risk reduction of 41%, absolute difference 3.2%, P=0.0314). As in ABCSG-12 trial, the benefit was in both local and distant recurrence (0.4% *vs.* 1.9% and 3.8% *vs.* 5.6%, respectively). Finally, AZURE trial (23) randomized 3,360 patients to receive neoadjuvant chemo- or endocrine therapy with or without zolendronate in neoadjuvant (every 3–4 weeks for six administrations) and adjuvant (three-monthly for eight administrations and then 6-monthly for five administrations) setting, consecutively. The primary endpoint was the comparison of DFS. After a median follow-up of 59 months, there were no differences in DFS between the two arms (HR 0.98, P=0.79) (23). Intriguingly, in the subgroup of women in postmenopausal status for more than five years, there was an improvement on OS (HR 0.71, P=0.017). This can explain the differences between the results of the AZURE trial and the ABCSG-12 trial, in which all enrolled patients received ovarian suppression with goserelin. A possible hypothesis could be that bisphosphonates act better with low oestrogen levels (24).

The NSABP-B34 trial (25) (clodronate *vs.* placebo for three years in adjuvant setting) was a multicentre, randomised, double-blind, placebo-controlled trial

conducted on 3,323 patients with early (stage I–III) BC. Patients were randomly assigned to receive after surgery either oral clodronate 1,600 mg daily for 3 years or placebo. The primary endpoint was DFS rate. DFS did not differ between the two arms (286 events in experimental arm versus 312 in placebo arm, HR 0.91, 95% CI: 0.778–1.07, P=0.27), and there was no difference even in OS (HR 0.84, 95% CI: 0.67–1.05, P=0.13).

However, looking only at women over the age of 50, in the experimental arm there was a statistically significant increase in DFS (HR 0.75, 95% CI: 0.57–0.99, P=0.045), in the time without bone metastases (HR 0.62, 95% CI: 0.40–0.95, P=0.027), but not in OS (HR 0.80, 95% CI: 0.61–1.04, P=0.094) (25).

Authors reported a suboptimal rate of non-adherence in the clodronate group (44% of withdrawals from treatment), possibly due to gastrointestinal side-effects. In our opinion, this is a major problem of the trial that can limit the value of its results. Furthermore, 23 patients in the experimental group and 12 in the placebo group experienced hepatic dysfunction ≥ grade 3. The authors also described a single case of osteonecrosis of the jaw in the experimental group. The limited magnitude of this study does not allow definitive conclusions to be drawn.

Final results from the SUCCESS trial (NCT02181101—adjuvant zolendronate for two versus five years) are awaited and could further clarify the role of bisphosphonates in the adjuvant setting as prevention of BM.

In metastatic setting, no trials demonstrated an impact of bisphosphonates in OS, but they could reduce the risk of skeletal events, reduce the bone pain and improve the quality of life (4,26). The efficacy of bisphosphonates to reduce the risk of SRE has been confirmed by a Cochrane analysis in which bisphosphonates was compared with placebo or no treatment in patients with BC BM. The reduction of the SRE risk was 14%, and there was a reduction of bone pain (4).

Bisphosphonates can also exert some indirect antitumor effects in the bone milieu, as suggested by some preclinical studies.

In the bone marrow microenvironment, a possible sanctuary for disseminated tumor cells that can evade systemic anticancer therapies and lay dormant for long periods, bisphosphonates might alter the levels of several growth factors (27,28).

Moreover, bisphosphonates reduce skeletal tumor burden in several preclinical models of bone metastasis from different solid tumors, including BC. This reduction can be attributed mainly to the antiresorptive activity of these drugs (29).

In particular, an interesting preclinical study (30) showed that an analogue of risedronate (NE-58051) with a 3,000-fold lower bone antiresorptive activity, do not inhibit BC BM cells or bone tumor burden, suggesting that the antitumoral activity of bisphosphonates is mainly due to inhibition of osteoclast-mediated bone resorption.

A retrospective analysis of phase III trials using zolendronate showed that in patients with elevated levels NTX (N-telopeptide of type I collagen), a bone-resorption marker, the normalization during 3 months of zoledronate correlates with an improvement on OS (9 months) (31). Another possible explanation could be that the survival benefit can be derived from the reduction of skeletal morbidity (such as fractures) rather than a direct anticancer effect.

The optimal frequency of bisphosphonates administration is still debated and has been investigated by several trials. Among these, we want to mention two trials that directly compared a 12-week schedule with a 4-week schedule. The OPTIMIZE-2 trial was a prospective, randomized, double-blind, multicenter phase 3 trial in which 416 women were randomized to receive zolendronate every 4 weeks or every 12 weeks, while 13 patients received placebo. The primary endpoint was the SRE rate. Secondary endpoints included time to first SRE and skeletal morbidity rate. After 1 year of follow-up, there was a difference in events of 1.2% (22% in the 4-week arm, 23.2% in the 12-week arm, non-inferiority P=0.02). The time to first SRE was not statistically different (HR 1.06, 95% CI: 0.70–1.60, P=0.79). The safety profile was comparable between the two arms (32). ZOOM trial was a non-inferiority, phase 3, multicenter trial that randomized 425 patients with BC BM with completed 12–15 months of monthly zolendronate to receive zolendronate (4 mg) every 12 or every 4 weeks. The primary endpoint was SRE rate. After one year of follow-up, the difference between the two arms was 4% (26% in 12-week arm, 22% in 4-week arm). The Authors concluded that the 12-week schedule was non-inferior to the 4-week schedule (33). From a cost-effective point-of-view, the 12-week schedule is a reasonable alternative to the 4-week schedule (34). Actually, the guidelines of the National Comprehensive Cancer Network (NCCN) (26) and ESMO (9) recommend to switch to a 12-week schedule after 1 year of monthly treatment with zolendronate. The duration of the treatment with bisphosphonate is not clear, and it depends of tolerability and toxicity.

Denosumab is an IgG2 monoclonal antibody that inhibits the RANKL-RANK interaction binding to receptor activator of nuclear factor k-B ligand (RANK) and preventing osteoclast formation and survival (35). Like bisphosphonates, denosumab has also been explored in the adjuvant setting of BC as a potentially preventive drug for BM, with discordant results. The ABCSG-18 trial randomized 1,711 postmenopausal patients with early luminal BC to receive denosumab 60 mg every 6 months or placebo. The primary endpoint was the rate of clinical fractures. Results showed a significant reduction of clinical fractures (11.15 with denosumab, 26.2% with placebo, HR 0.50, 95% CI: 0.30–0.65) (36), and a modest improvement in DFS in the denosumab arm (5-year DFS: 89.25 with denosumab *vs.* 87.35 with placebo, HR 0.82, 95% CI: 0.69–0.98, absolute gain 1.9% at 5 years and 3.15% at 8 years) (37). Conversely, D-CARE trial (38) found no positive effect on either its primary endpoint of BM free-survival or DFS, the secondary endpoint. In particular, D-CARE trial randomized 4,509 pre and post-menopausal patients with non-metastatic BC with high risk of recurrence (nodal involvement at diagnosis, tumour size >5 cm or locally advanced disease) to receive monthly denosumab 120 mg for six doses or placebo. After a median follow-up of 67 months there were no significant differences in BM free survival or DFS (HR 0.97 and 1.04 respectively, with a non-significant P value). Moreover, no subgroup has benefit from denosumab. The study population of the D-CARE trial was more homogeneous and significant different from the ABCSG-18 trial, in which 75% of patients received chemotherapy in early setting and 100% received aromatase inhibitors. This could partly explain the differences in results between the two trials. Data on role of denosumab in adjuvant setting is still uncertain and bisphosphonates should remain the standard of care.

In metastatic setting, the comparison between denosumab and zoledronate has been investigated in a large trial that randomized 2,046 patients with BC BM (39). The trial showed an improvement in time to first on-study SRE (HR 0.82; 95% CI: 0.71–0.95, P<0.001 non-inferiority; P=0.01 superiority) and in reducing risk of multiple SRE (P=0.001) in denosumab arm with a dose of 120 mg monthly. OS was the same between arms (HR 0.95; 95% CI: 0.81–1.11, P=0.49). The optimal duration of the BC BM treatment with denosumab is not still clarified. Generally, the use of denosumab in clinical trial has been evaluated up to two years or until unacceptable toxicity.

As with zoledronic acid, schedules with different dosing intervals were also explored for denosumab, in order to reduce side effects and maintain the same efficacy. The SAKK 96/12 trial (NCT02051218) is currently in progress, with the aim to test the hypothesis that the administration for 12 weeks is not inferior to administration every 4 weeks in terms of first on-trial SSE. The estimated enrollment is 1,380 patients with BC or prostate cancer, and the estimated study competition date is December 2022. Preliminary data published in the form of abstracts and presented in the San Antonio Breast Cancer Symposium 2018 (40) show that denosumab-related hypocalcemia is less frequent with administration every 12 weeks.

The side effects of bone-modifiers such as bisphosphonates and denosumab are similar: osteonecrosis of jaw, nephrotoxicity and hypocalcemia are the most frequent. The incidence of osteonecrosis of jaw (ONJ) is 0.6% to 6.25 in patients with BC BM treated with bisphosphonates and the incidence is similar in patients treated with denosumab (39). The most important risk factors for ONJ are inflammatory dental or alveolar diseases, long exposition to therapy with bone modifiers (41), glucocorticoid or anti-angiogenic therapies (42). The treatment with bisphosphonates or denosumab should be delayed for 2–3 weeks after invasive dental procedures (43). Nephrotoxicity is more frequent with zolendronate than with denosumab (39). Renal failure related to bisphosphonate is dose-depended. Dose adjustment should be evaluated according to the grade of renal impairment and the clearance of creatinine. In case of decrease of renal function during bisphosphonate therapy, drug should be withheld until renal function returns to within 10 percent baseline (43).

Hypocalcemia and hypophosphatemia are common side effects during treatment with denosumab (39,44). Thus, calcium and vitamin D supplementation is recommended in order to prevent hypocalcemia. More rarely, bone modifiers can cause cardiac arrhythmias like atrial fibrillation and supraventricular tachycardia (45), skin reaction, ototoxicity (46) or infections (47).

Radionuclides

Systemic radionuclide therapy can be used to manage pain derived from BM after failure of systemic analgesics or radiotherapy, especially when the side effects correlated to high dose analgesics become intolerable.

Main contraindications are asymptomatic bone lesions,

pure osteolytic lesions or inadequate marrow reserve, spinal cord compression, high risk of fracture or pathologic fracture of weight bearing bone, renal failure, pregnancy and breastfeeding (48). Furthermore, since radionuclides have an action latency from 1 to 4 weeks, patients' prognosis should be more than 3 months.

The general principle of functioning of radionuclides is deliver local radiation by emitting beta particles trying to avoid deep radiation of bone marrow. Radionuclides approved and commonly used in radionuclide therapy are Strontium-89 hydrochloride (Sr-89), samarium-153 lexidronam (Sm-153) and rhenium-186 hydroxyethylidenediphosphonate (Re-186), while Phosphorus-32 (P-32) is outdated due to severe myelotoxicity.

Other clinical trials evaluating the palliation potential of other radionuclides such as tin (^{117}mSn)-diethylenetriaminepentaacetate (DTPA), sodium (^{33}P)-phosphate, rhenium (^{188}Re)-hydroxyethylidenediphosphonate (HEDP), lutetium (^{177}Lu)-EDTMP, and radium (^{223}Ra)-chloride are ongoing.

The most significant toxicity is characterized by transient myelosuppression with neutropenia, anemia and, less frequently, thrombocytopenia (48).

In patients with BC BM, a clinical benefit rate in terms of pain reduction of 70–80% has been reported after 1 week of intravenous ^{53}Sm-EDTMP administration with prolonged responses of up 12 months (49).

Serafini and colleagues conducted a comprehensive review of data about clinical response rate on systemic radionuclide therapy; in summary, the response rate for BC BM ranged from 50% to 92% (50), and these results were confirmed by other authors (51,52).

Following the observation that response duration is longer in patients treated earlier with radionuclides, it was hypothesized that radiopharmaceuticals could play a role in eradicating micrometastatic disease localized in bone marrow (53). This tumoricidal effect appears to be enhanced when radiopharmaceuticals are administered in synergy with other treatments such as external-beam radiotherapy and/or systemic therapy (chemotherapy or endocrine therapy) (54,55). However, these approaches could be burdened with greater toxicity, especially haematological. The multi-modality approach using bisphosphonate, chemotherapy and radiopharmaceutical has been shown to be superior in terms of symptoms control and prolonged survival rather than chemotherapy or radiopharmaceuticals alone (56).

Another strategy to increase the rate and duration of clinical responses is the administration of repeated doses of radionuclides. Kasalický and colleagues reported prolonged response duration in patients with BC BM after receiving multiple ^{89}SR administrations compared with patients who had received a single administration (3.08±0.48 versus 5.33±2.36 months) (57).

New drugs

In the last few decades, a large number of new molecules have been investigated as promising drugs for BC BM therapy. In vitro, Dasatinib, a tyrosine kinase used in chronic myeloid leukemia, has been seen as capable of inhibiting osteoclastogenesis (58). Its role on treatment of BM from BC has been evaluated on SWOG S0622 trial, a phase II clinical trial aimed to determine an improvement on PFS and a decrease of serum bone turnover markers (59). Seventy-nine patients with BM from BC were enrolled. After a median PFS of 12.6 weeks, there were no significant differences in PFS, without statistically significance (P=0.85) (59). Therefore, this trial failed to demonstrate an advantage of dasatinib in this cohort of patients, but further studies with wider accrual should be conducted.

In a phase 1 study, another tyrosine-kinase, saracatinib, was seen to reduce bone resorption markers up to 88% from baseline after 24 h with no effect on bone formation markers and without serious adverse events (60). These results are similar to results derived from previous trials on bisphosphonates in in women with BM from BC. Data on the clinical efficacy of saracatinib are still early and need further validation in phase 2 and 3 clinical trials.

Other promising agents are curcuminoids, which could prevent tumour growth-factor beta (TGF-β) induction of parathyroid hormone-related protein (PTHrP) reducing osteolytic bone reabsorption (61). The efficacy of this class of drugs in reducing osteolysis resulting from BM of BC has been confirmed in *in vivo* murine models (62). In clinical setting, a phase I trial has been conducted to investigate the feasibility and safety of docetaxel and curcumin in patients with BM from BC (63). This trial enrolled 14 patients that received 6,000 mg per day of curcumin, for 7 days every 3 weeks in combination with docetaxel. Preliminary data on efficacy are encouraging and a phase II clinical trial on curcumin plus docetaxel versus docetaxel single-agent recently terminated, but data are not yet published (NCT00852332).

Some monoclonal antibodies that block PTHrP or proteasome inhibitors that can directly interfere with the process of bone metastases by tumor cells are also

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promising.

An interesting new strategy is the combination of cytotoxic agents with antigen-specified nano-particles as vectors, e.g., micelle with $\alpha v \beta 3$-MP-docetaxel. This nanoparticle recognizes $\alpha v \beta 3$ integrin in BC cells in the bone and can carry the chemotherapeutic drug within the BM with less systemic toxicity (64).

Teriparatide is a bone-anabolic agent currently used in the treatment of osteoporosis. It is able to increase the bone formation and some authors have also reported a suppression of the growth of myeloma lesions in bone (65). The authors suggest that teriparatide can be effective also in solid tumor metastases, including BC.

Abaloparatide is a homologue of the parathyroid hormone (PTH) and the parathyroid hormone-related protein (PTHrP) (66). It is able to perform an anabolic action on the bone, while it has a limited effect on bone resorption. The exact pharmacokinetics and pharmacodynamics mechanisms of the abaloparatide are better described elsewhere (66). Its clinical use is currently limited to therapy of osteoporosis, however it is a promising agent for the treatment of hypercalcemia. To our knowledge, there are no ongoing trials on the role of abaloparatide in the treatment of BC BM.

Loco-regional treatments

In the case of risk or in the presence of a skeletal segment fracture, surgery is the first choice option, especially in the case of spinal compression, where the decompression treatment is a urgency. In case of impossibility or contraindication to perform surgery, vertebroplasty can be a good alternative to surgery for vertebral compression fractures. It is minimally invasive and there is clinical evidence for improvement in pain and physical function (67). Another therapeutic option is radiotherapy (RT) (25,68), which also has a primary role in treating the pain of individual bone lesions when systemic pain therapy is not adequate. In this case, one single fraction with 8 Gy is recommended, because dose intensification or fractionated irradiation does not result in a better analgesic effect (69).

Biomarkers

The detailed description of the molecules and physiological or pathophysiological processes of normal or metastatic bone metabolism is beyond the scope of this review and is well described elsewhere (70).

Ad ideal biomarker of BC BM should have: a diagnostic role (in terms of detection of presence of BM), an early prognostic value (e.g., estimate the risk of a patient with early BC to develop BM) a late prognostic value (e.g., estimate the risk of BM progression or develop SRE) or a predictive value (e.g., estimate the probability of response to targeted treatments for BM).

Some bone turnover markers (BTM) have been investigated as diagnostic markers of BC BM. For example, the tartrate resistant acid phosphatase (TRACP) and the pro-collagen type 1 N-terminal pro-peptide (P1NP) were seen to increase significantly in the presence of BM, especially when BMs were >7 , with discordant results (71,72). The receptor activator of nuclear factor KB-ligand/ osteoprotegerin ratio was also reported to be significantly increased in BC BM, with a sensitivity and specificity of 73% and 72%, respectively (73). However, specificity, sensitivity and diagnostic efficacy are suboptimal and BTM do not yet have a diagnostic role in routine clinical practice, where imaging techniques are preferred.

Some BTMs such as serum bone alkaline phosphatase (sBALP) and urinary N-telopeptide of type 1 collagen (uNTX) have been investigated as prognostic markers. Coleman and colleagues (74) reported a significant correlation between sBALP and uNTX and the occurrence of SRE in 1,824 patients under zolendronate or pamidronate for BM from different malignancies. Similarly, Brown and colleagues (75) demonstrated a significant correlation between high sBALP and uNTX levels at baseline and the risk of SRE in patients under bisphosphonates. Conversely, in patients with high baseline levels of uNTX, the normalization of this value during the bisphosphonate treatment was significant correlated with less SRE or death risk (76). Moreover, in patients with NTX levels within the normal range throughout the treatment duration has a reduction (40–68%) of the death or SRE risk ($P<0.0005$) as compared to those with raised NTX levels (77).

Few trials have investigated the potential role of BTM in predicting the efficacy of bone modifiers such as bisphosphonates or denosumab in BC BM. Most of the data derives from randomized clinical trials that included patients with different malignancies, including BC. Coleman and colleagues (78) reported that in patients with various malignancies or multiple myeloma and with baseline NTX >100 nmol/mmol creatinine, there was a significant reduction of death risk of 31% ($P=0.0028$) if a zolendronate treatment was administrated. However, these results should be validated on larger populations with BC BM. Furthermore, some concomitant treatments or intrinsic

features of the patients (e.g., age, sex, comorbidity etc.) as well as seasonal variations can interfere with the BTM levels influencing the evaluation (70,79).

Several studies have tried to identify a significant genomic signature for increased risk of BC BM. A number of genes coding for membrane molecules involved in protein binding (80), or genes for interleukin 1-beta (IL-1β) (81) or for interleukin 1 receptors (82), or genes coding for zinc-finger proteins (such as ZNF217) (83) were identified, all significantly related to a greater tumour cell osteotropism. However, these data derive exclusively from preclinical studies, and there are no significant validations in the clinical setting to date. In the analysis of breast tumour samples from 724 patients enrolled in the AZURE trial (mentioned above), high expression of macrophage-capping protein (CAPG) and PDZ domain-containing protein member 1 (GIPC1) was significantly correlated with the risk of development of BM (P<0.001) and with the efficacy of zolendronate in preventing BM (P=0.008) (84). Thus, the combined CAPG/GIPC1 biomarker is one of the most promising biomarkers of response to bisphosphonates, although further and larger studies are needed to validate its use in current clinical practice.

For a long time the CA 15-3 tumor marker was used as a biomarker of mBC. It is not bone-specific and is not recommended as marker of surveillance due to low sensitivity (30%) (85).

Currently there are no bone-specific biomarkers used in clinical practice (86). In fact, the American Society of Clinical Oncology guidelines do not recommend use of biochemical biomarkers as treatment monitoring, due to lack of strong evidence deriving from published studies (43).

Conclusions

The optimal management requires a multidisciplinary approach that includes medical and radiation therapy, orthopaedic surgery, interventional radiology, nuclear and palliative interventions to control symptoms, avoid SREs and improve quality of life.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cco.2020.01.07). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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