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Review

Bone health in breast cancer patients: A comprehensive statement by CECOG/SAKK Intergroup

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ABSTRACT

Bone is the most common site of distant metastases in breast cancer that can cause severe and debilitating skeletal related events (SRE) including hypercalcemia of malignancy, pathologic fracture, spinal cord compression and the need for palliative radiation therapy or surgery to the bone. SRE are associated with substantial pain and morbidity leading to frequent hospitalization, impaired quality of life and poor prognosis. The past 25 years of research on the pathophysiology of bone metastases led to the development of highly effective treatment options to delay or prevent osseous metastases and SRE. Management of bone metastases has become an integral part of cancer treatment requiring expertise of multidisciplinary teams of medical and radiation oncologists, surgeons and radiologists in order to find an optimal treatment for each individual patient.

A group of international breast cancer experts attended a Skeletal Care Academy Meeting in November 2012 in Istanbul and discussed current preventive measures and treatment options of SRE, which are summarized in this evidence-based consensus for qualified decision- making in clinical practice.

Introduction

During the last two decades bone health has emerged as an important topic in the management of early as well as metastatic breast cancer patients (MBC). Bone is the most common site of distant metastases in women with breast cancer, affecting some

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65–70% of patients during the metastatic phase of the disease. More than two thirds of these patients will suffer from skeletal related events (SRE) including pathologic fracture, bone surgery, spinal cord compression, palliative radiation therapy to bone, and hypercalcemia of malignancy. Less commonly, bone metastases can invade through the bone marrow cavity and disrupt hematopoiesis leading to bone marrow failure [1]. Nearly 20% of patients with MBC have "bone only disease" without involvement of other organs. Although this particular subgroup has a relatively favorable outcome in terms of overall survival, still the SRE frequently encountered in these patients are ultimately associated with substantial morbidity that leads to severe pain, loss of autonomy, impairment of quality of life, frequent hospitalization, and marked increase of health care costs [2].

In early breast cancer patients, bone health may also be compromised as a result of the adjuvant treatment, which is known to enhance the process of bone resorption. The increased use of aromatase inhibitors in post menopausal women and the use of adjuvant chemotherapy and/or ovarian-ablative therapy in the premenopausal women have been reported to induce accelerated bone loss with subsequent osteoporosis and increasing risk for fractures [3,4].

The extensive research on bone homeostasis and pathophysiology of bone metastases over the past 25 years has identified osteoclastic activation as the main cellular mechanism responsible for both osteoporosis and osteolytic metastases. This has led to the development of drugs that can effectively maintain bone health in early breast cancer, and reduce SRE in patients with osseous metastases.

A group of international breast cancer experts including medical and radiation oncologists, radiologists and surgeons attended a Skeletal Care Academy Meeting in November 2012 in Istanbul. The meeting was organized by CECOG (Central European Cooperative Oncology Group) in cooperation with SAKK (Swiss Group for Clinical Cancer Research). The main goal of the meeting was to discuss recent progress in the treatment and prevention of SRE in patients with bone metastases from breast cancer. This statement summarizes the key issues in this area and provides an international evidence-based consensus for qualified decision- making in the treatment of bone metastases.

Diagnostic imaging

Imaging plays a major role in the identification of skeletal metastases. Four modalities are used in clinical practice: plain radiography, radionuclide bone scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI).

Plain X-rays are commonly used as initial evaluation in patients with bone pain and in the assessment of the risk for pathologic fractures. However, they have a very low sensitivity and specificity as lesions only become visible when 50% of the bone mass are already lost [5].

Radionuclide bone scintigraphy is widely used in screening for suspected metastases, because it provides visualization of the entire skeleton. 99mTc-methylene diphosphonate (99mTc- MDP) is the most commonly used tracer. Intense accumulation occurs in areas of increased osteoblastic activity and of increased blood flow [6]. However, in pure osteolytic lesions and in fast growing bone metastases false negative results are common [7]. Furthermore, bone scintigraphy lacks anatomic resolution, which increases the difficulty in distinguishing tumor from non-tumor uptake (e.g. traumatic, inflammatory and degenerative processes) and may lead to false-positive results.

Suspicious scintigraphic findings, which appear equivocal on radiographs, require further evaluation with computed tomography (CT) or magnetic resonance imaging (MRI). Both imaging techniques are able to better display anatomic and pathologic changes (Fig. 1).

CT is more sensitive in detecting bone metastases than plain radiographs. It offers high bony detail and can detect subtle osseous metastases as well as – though to a lesser extent than MRI – the early metastases in bone marrow [5].

MRI is a very sensitive technique for detecting bone marrow metastases even before the osseous infiltration occurs as well as for spinal cord compression [8]. Furthermore, MRI offers a way to visualize the lesions with good spatial and contrast resolution, and without using ionizing radiation [9].

With the use of CT or MRI the local extent of metastatic disease can be determined prior to the planning of palliative surgery or radiotherapy. Both modalities are used in image-guided interventions such as radiofrequency ablation or laser-induced thermography [10].

Fluoro-deoxy-glucose positron emission tomography (FDG-PET) detects the tumor directly by its metabolic activity, rather than indirectly by showing tumor involvement due to increased bone mineral turnover [11] and has shown superiority to bone scintigraphy in the detection of metastases [12]. It is more sensitive in detecting osteolytic lesions, but less sensitive for detection of osteoblastic lesions than bone scintigraphy [13].

In the recent meta-analysis of seven trials and 668 patients with breast cancer and bone metastases, the higher sensitivity of FDG-PET/CT compared to bone scintigraphy was demonstrated (0.93 and 0.81, respectively) [14]. The specificity of the two methods was comparable (0.99 and 0.96, respectively). As an older meta-analysis showed sensitivity of FDG PET to be only 0.81 [15], the authors concluded that integration of CT scan to FDG-PET improved the sensitivity of the combined method.

Limitations of FDG-PET – in addition to higher cost and limited availability – exist in regard to histological subtypes of breast cancer. Invasive lobular breast cancer has lower FDG uptake compared to invasive ductal carcinoma (median SUV 3.4 vs. 6.6. for lobular and ductal type, respectively; $p = 0.0003$), which is of relevance for clinicians when deciding on the type of diagnostic imaging both at staging and in metastatic disease [16].

Increasing interest exists for PET-CT in assessment of treatment response. In abstract presented at San Antonio Breast Cancer Symposium in 2013 (SABCS), Mongomery et al. reported that SUV changes in FDG-PET during the treatment were predictive of time to progression (TTP). In contrast, SUV changes in 18 F-fluoride PET did not show a correlation with TTP [17].

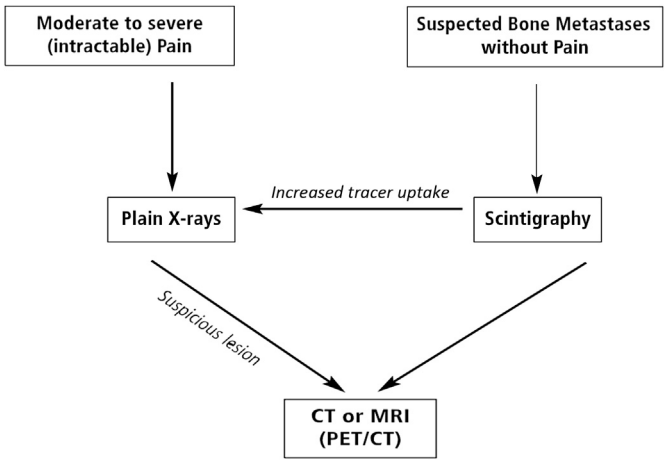

Fig. 1. Algorithm for radiological detection of bone metastases.

Whole-body MRI with diffusion-weighted imaging (DWI) is a novel approach in which the MRI signal intensity is influenced by self-diffusion of water molecules [18]. MR-DWI seems to be particularly useful for the distinction of benign and malignant vertebral compression fractures and may be able to predict treatment response to chemotherapy based on assessments of cellularity and tumor vascularity, which often precede morphologic alterations [19–22].

Treatment of bone metastases and SRE

The optimal management of bone metastases is rather complex, requiring a multidisciplinary team of medical oncologists, radiotherapists, orthopedic surgeons and radiologists.

The therapeutic objectives should entail maximal control of pain, stabilization of the affected bone, preservation/restoration of patient independence, and securing local tumor control. The choice of treatment is influenced by several factors such as severity of skeletal symptoms, location and extent of the osseous lesion, presence of symptomatic visceral metastases, performance status of the patient and vital organ functions. Current treatment options include a variable combination of radiation therapy, surgery, vertebroplasty/balloon kyphoplasty and systemic therapy with bone-modifying agents.

Radiotherapy

Radiotherapy is the mainstay in the treatment of bone metastases, which provides an effective and non-toxic therapeutic tool for almost all patients. It is indicated for pain relief, local tumor control, prevention/control of pathological fractures and neurologic deficits (e.g. spinal cord compression). For localized pain, radiotherapy is a well-accepted treatment modality with a 60–80% likelihood of overall pain relief reported [23–25].

A complete response is usually defined as complete freedom from pain, while partial response is defined as improvement by two points on the visual analog scale without increase of pain medication, or a reduction of the pain medication by 25% without increase of pain on the visual analog scale [26].

Numerous clinical studies have compared different radiation fractionation regimens for 3 main end points: pain response, the rate of re-irradiation due to recurrent pain, and the rate of pathological fractures following radiotherapy. For pain relief, randomized trials and meta-analyses have unequivocally shown that single-fraction radiotherapy with 1 × 8 Gy is as effective as multi-fraction regimens such as 5 × 4 Gy, 6 × 4 Gy or 10 × 3 Gy [23,24,27–30].

In a recent meta-analysis which included 25 randomized controlled trials the overall response rate documented was similar in patients receiving single fractions (1696 of 2818; 60%) and multiple fractions (1711 of 2799; 61%) [30]. The rates of complete response were seen in 620 of 2641 (23%) patients in the single fraction arm and in 634 of 2622 (24%) patients in the multiple fraction arm. Pathological fracture rate was the same in the two arms, but spinal cord compression trended insignificantly in favor of multiple fractions ($p = 0.13$). However, the likelihood of requiring re-irradiation was the only significant advantage that favored protracted radiation regimen over a single fraction (2.6-fold greater in the single fraction arm; 95% confidence interval: 1.92–3.47; $p < 0.00001$) [30].

Another potential benefit of multiple fraction regimen is related to post treatment bone re-calcification. In a prospective study, Koswig and Budach demonstrated a significant increase in bone density after 10 × 3 Gy compared with 1 × 8 Gy (173% versus 120%, $p < 0.001$). However, the authors did not correlate the data to pathological fracture rates [31].

In case of pain recurrence after a single fraction radiation therapy, re-irradiation is indicated, often with no technical concerns. In such cases the response rates after re-irradiation are usually similar to those observed after the first course of radiotherapy. In a retrospective series of 105 patients, the overall response rate was 87% [32], while in another study, the overall response rate to re-irradiation was 73% (80/109), and the complete response rate was 31% [33]. In the less likely event of pain recurrence after the 10 × 3 Gy radiation course, re-irradiation is still feasible, but it should consider the radiobiological rules for critical organ tolerance, notably the spinal cord. In these cases, high-precision radiotherapy techniques (e.g. 3D-conformal, stereotactic body radiation therapy [SBRT], dynamic arc radiotherapy, and intensity-modulated radiotherapy [IMRT]), are certainly indicated in order to guarantee maximum sparing of normal tissues exposure and reduce potential late toxic effects.

SBRT represents a very useful radiation modality for spinal metastases, which allows delivering of high doses of radiation (20–30 Gy) in 1–5 fractions to spinal metastases while sparing the spinal cord a toxic radiation dose [34]. SBRT may be an ideal treatment in patients with bone only oligometastases, which can potentially be cured with local therapies. In such cases the very high response rate achieved by SBRT (around 80%) may provide an unprecedented chance for long-term survival in these patients [35].

Toxic effects of radiotherapy

Radiation-related acute toxic effects depend essentially on the local sites to be irradiated and the extensiveness of the radiation portals, and to a lesser extent to the radiation treatment regimen. In the RTOG 97-02 trial the rate of acute toxic effects was significantly higher in the multiple fraction arm compared to the single fraction arm (17% versus 10%, $p = 0.002$) [36]. However, in a large meta-analysis, no significant differences in acute toxic effects was seen with multi-fraction radiotherapy compared with single-fraction radiotherapy [25]. Interestingly, several studies have shown that re-irradiation does not seem to significantly add to acute radiation toxicity. The most common acute side effects were skin reactions and gastrointestinal toxic effects such as nausea and/or vomiting and diarrhea. A transient aggravation of bone pain ('pain flare') may occur during radiotherapy. In clinical trials pain flares occurred in 14–44% of patients [37,38]. In a non-randomized phase II trial dexamethasone (at 8 mg, administered just before radiation therapy, and for three consecutive days after treatment) has been shown to be effective in the prophylaxis of radiation induced-pain flares [39]. Hematologically, localized field radiotherapy to the bones is generally considered as a safe treatment; still, if several metastatic sites have to be irradiated simultaneously, radiotherapy would have a profound effect on bone marrow function that may compromise the administration of subsequent chemotherapy.

Some recent studies have encountered vertebral compression fractures (VCF) as a potential complication appearing several months after SBRT [40–42]. In one study of 93 patients, SBRT has been associated with a significant risk (20%) of VCF [43]. Risk factors for VCF include age >55 years, a pre-existing fracture, low bone mineral density and baseline pain. It has been suggested that these risk factors should be carefully assessed and all candidate patients have to undergo prophylactic vertebral stabilization or augmentation procedures prior to treatment by SBRT. Further studies are needed to determine the radiation dose tolerance of the vertebral body to prevent vertebral collapse in patients with clinical risk factors for pathologic fractures. Meanwhile oncologists should be

Table 1
Mirels' Score for assessment of pathological fracture risk [49].

Variable	Risk Score		
	1	2	3
Site	Upper limb	Lower limb	Peri-trochanteric
Pain	Mild	Moderate	Aggravated by function
Lesion type	Blastic	Mixed	Lytic
Size relative to bone diameter	<1/3 of cortex	1/3 to 2/3 of cortex	>2/3 of cortex

The four variables are scored between 1 and 3 giving a total score out of 12.

Mirels' recommendations

Mirels' score	Clinical recommendation
≤7	Radiotherapy and observation
8	Use clinical judgment
≥9	Prophylactic fixation

alert to the potential risk of bone toxicity caused by this novel treatment.

Surgery

In the past three decades, advances in orthopaedic techniques and implants have expanded the treatment options for patients with skeletal metastases allowing for reconstruction of even the most challenging pathologic fractures [44].

Clear indications for operative interventions in metastatic bone disease are pathologic fractures of long weight-bearing bones and spinal cord compression with rapidly progressive neurologic deficit. Further indications are worsening of neurologic deficit during radiotherapy or when the spinal cord tolerance is reached.

Major goals of an operative management of bone metastases are relief of intractable pain that is non-responsive to conservative treatment and restoration of mechanical stability and ambulatory function. Additionally, aggressive treatment of solitary skeletal metastases may improve long-term survival in selected patients [45].

A meta-analysis of uncontrolled cohort studies concluded that surgery should be considered as a primary treatment option for patients with metastatic spinal disease, followed by radiotherapy [46]. In the surgical group patients were 1.3 times more likely to be ambulatory after treatment and twice as likely to regain ambulatory function than in the radiation group. Furthermore, pain relief was also higher in the surgical group compared to the radiation therapy group (85% versus 64% respectively, $p < 0.001$) and the same applied to sphincteric control (66% versus 26%, respectively) [46]. In a randomized trial in patients with spinal cord compression caused by metastatic lesion, decompressive surgery followed by radiotherapy was compared to radiation alone. The primary end point – ability to walk – was significantly higher in the surgery group [47].

A separate analysis of the same trial showed that the benefit of the surgery was limited to the patients younger than 65 years [48]. Preservation of ambulatory function in those patients was significantly higher if treated with surgery compared to radiation alone ($p = 0.002$). For patients older than 65 years there was no difference in ambulation time among two treatment groups, indicating importance of careful patient selection if more intensive treatment is considered [48].

In case of an impending pathological fracture, surgical stabilization should be considered since prophylactic fixation of a lesion prior to an actual pathological fracture prevents pain and loss of function, which are associated with pathologic fractures.

The risk of pathological fracture can be assessed with Mirels' score [49]. The composite weighted scoring system is based on four variables believed to contribute to pathologic fracture risk: location, radiographic appearance of the lesion, size and pain level (Table 1). Lesions with scores of 7 or less have a low risk of fracture. Scores of 8 and higher predict high risk and require referral to an orthopaedic surgeon for consideration of prophylactic stabilization [50,51].

Mirels' system is based on plain radiographs and clinical examination. It has been shown to be reproducible and valid as well as more sensitive than clinical judgment.

A variety of techniques, including prosthetic reconstruction or a combination of internal fixation with polymethyl methacrylate (PMMA), provide immediate fixation and stability [43]. Postoperative long-course radiotherapy should be utilized in all cases after the wound has healed to arrest local tumor growth, permit bone repair, and prevent re-growth of tumor around the fixation device [45,52,53].

Vertebroplasty and balloon kyphoplasty

Vertebroplasty (VP) and balloon kyphoplasty (BKP) are interventional techniques performed by surgeons, anesthesia pain specialists, and interventional radiologists used to stabilize vertebral compression fractures and reduce pain. Vertebroplasty is a procedure where bone cement, usually PMMA, is injected into the vertebral body. In the kyphoplasty procedure, a balloon is first inserted into the vertebral body, followed by inflation and then deflation, before cement is added. Those procedures are indicated in patients with vertebral compression fractures (VCFs), which occur in up to 30% of patients with bone metastases [54]. VCFs can cause significant acute and long-term pain, can compromise pulmonary function, and impair activities of daily living and mobility. There is a good body of evidence that balloon kyphoplasty in these patients is well tolerated, provides rapid pain relief, and improves patients' functional capacity, quality of life, and vertebral height compared with pre-treatment status for up to 2 years after the procedure. The main adverse events are back pain, which occurs in less than 10% of the patients, and cement extravasation, which is more common in VP (up to 40%, depending on the series) than in BKP (up to 13%) [55]. Of notice, cement leaks are rarely symptomatic [56].

Both procedures have been subject to controversy after two randomized trials in patients with painful osteoporotic fractures failed to show pain improvement following vertebroplasty [57,58]. However, two trials published shortly afterwards demonstrated a significant pain reduction in patients with osteoporotic fractures after treatment with BKP [59] and VP [60]. In a recent systematic review the authors found that there was a benefit of vetrebroplasty and kyphoplasty compared to non-surgical treatment [61].

In the recently published CAFE study, 134 patients with painful VCFs from bone metastases were randomly assigned to BKP ($n = 70$) or non-surgical management ($n = 64$) [62]. Compared to the baseline status, BKP was shown to rapidly reduce pain and improve the back-specific functional status by almost 50% ($p < 0.0001$) versus no improvement in the conservative group.

Percutaneous VP has a similar efficacy and safely profile as BKP, with 70–90% of patients reported to have markedly reduced pain and improved function.

Given the safety and efficacy of these minimally invasive procedures, they should be considered as part of a multidisciplinary approach to patients with painful VCFs.

Radiopharmaceuticals

Radionuclide therapy has emerged as an alternate modality for the palliation of bone pain in patients with multiple osseous metastases and predominantly osteoblastic lesions.

Radioactive agents are systemically administered and deliver focal radiation to sites of bone metastases through β-emission (strontium-89, samarium-153, rhenium-186) or α-particles (radium-223). These compounds have several advantages including convenience of administration and ability to treat multiple metastases simultaneously. Clinical studies as well as case series report pain response rates between 40% and 95% [63]. However, the vast majority of these studies and case reports have focused on pain due to osteoblastic bone lesions in prostate cancer [64]. Only several randomized trials enrolled subsets of patients with breast cancer [65–67].

In these small groups, response rates were quite promising, ranging from 44% to 92% and duration of pain relief lasting as long as 14 months [66].

In the only published randomized controlled trial of radionuclides for metastatic breast cancer patients were randomized to receive either 89 Sr or 186 Re-HEDP [66]. While pain response and duration were similar between groups, patients receiving 186 Re-HEDP obtained pain relief more quickly and recovered from transient myelosuppression significantly faster than did patients treated with 89 Sr.

Recently, the combination of Sm-153 oxabifore and denosumab proved highly effective in breast cancer patients with painful bone metastases and disease progression in spite of previous bisphosphonate therapy [68]. Pain relief occurred within 4.4 ± 1.25 days and the pain score decreased significantly from 7.8 at baseline to 0.2 ($p < 0.0001$) after six months of combined treatment. In one patient the number of metastases and intensity of radiotracer uptake was significantly reduced as documented on whole body scan. In four patients complete disappearance of osteoblastic lesions was observed.

While in these small studies all agents have shown to be safe and effective with repeated doses, large, randomized controlled trials are needed to confirm the usefulness of bone-seeking radionuclides for pain palliation in breast cancer patients [64].

Bone targeting therapies in metastatic breast cancer

Molecular basis of bone targeting therapy

One of the most peculiar aspects of bone physiology is known as bone remodeling, which is a dynamic process of continuous cycles of bone resorption and bone formation, required to preserve the bone mass and structural integrity, while maintaining mineral homeostasis [69]. Physiological bone remodeling entails a well-balanced interplay between osteoclasts, dissolving old bones; and osteoblasts; laying down new bones, so that the amount and contour of new bone deposition are always equivalent to what has been resorbed (balanced & coupled remodeling). At the molecular level, bone remodeling is primarily regulated by a complex interaction between the triad of RANK/RANK Ligand (RANKL)/Osteoprotegerin (OPG). RANK (Receptor Activator of Nuclear Factor-kappa B) is a surface receptor mainly expressed on mature osteoclasts and their progenitors [70,71]. Its primary function is to induce osteoclastogenesis and control calcium homeostasis [72]. RANK is activated when it binds to its cognate ligand (RANKL), which is expressed on the surface of osteoblasts and bone stromal cells. Signaling through RANK leads to differentiation of osteoclast progenitors, formation of mature activated osteoclasts and increased survival of activated osteoclasts. Stimulatory effects of RANKL on osteoclasts are opposed by OPG, which is also secreted by the osteoblasts and stromal cells, and functions as a soluble decoy receptor for RANKL [73]. OPG competes with RANK for RANKL, thus it prevents the RANKL–RANK interaction on the osteoclast cell membrane, leading to cessation of osteoclastogenesis and bone resorption. Conceptually, the level of osteoclastogenesis and bone remodeling is primarily regulated by the RANKL/OPG ratio, in as much as a relative increase of RANKL results in excessive bone resorption while a relative increase in OPG inhibits resorption [73].

Since bone is mainly composed of hard-mineralized matrix, it is more resistant to invasion and destruction by cancer cells, compared to other metastatic sites [74]. Therefore and in order to grow within the bone matrix, the cancer cells must recruit and activate osteoclasts, which are the most efficient cells to induce bone resorption. This provides the space in which cancer cells can grow and allows them to induce further cross talks with the different cellular and molecular components of the bone microenvironment, thus creating a milieu that is conducive for tumor invasion ("soil and seed hypothesis of bone metastases"). During the osteoclastic phase of bone remodeling a multitude of growth factors and cytokines is released from the bone matrix (e.g. TGF-β, IGF II and calcium ions). These cytokines can mediate several cellular and molecular interactions to support the survival of cancer cells within the bone matrix. Cancer cells – in return – are able to induce osteoclastogenesis through the release of many soluble mediators (e.g. IL-1, PTHrP). Interestingly, the vast majority of these osteoclastic activating factors induce bone resorption via the up-regulation of RANKL expression by osteoblasts and stromal cells, which results in enhanced RANKL to OPG ratio and excessive bone resorption [75]. This reciprocal feedback between cancer cells and bone microenvironment has been referred to as the "vicious cycle of bone destruction", in which osteoclasts are the key cellular player, whereas RANKL stands as the final effector of osteoclastogenesis. The cellular and molecular interactions between breast cancer cells and bone microenvironment are shown in Fig. 2.

Bisphosphonates

Identifying osteoclasts as the main cellular component in the development and progression of bone metastasis has promoted the use of bisphosphonates, which are potent inhibitors of osteoclastic bone resorption in the treatment of almost all types of bone metastases [3,76]. Bisphosphonates localize predominantly to skeletal areas of high bone turnover including osteolytic bone metastases [Hadji, 2011] [77]. The two negatively charged phosphonate groups give these compounds the ability to bind with a very high affinity to calcium ions within the hydroxyapatite crystals in mineralized bones [78,79], where they are concentrated for a very long half-life that may exceed one year (as in case of zoledronic acid) [80]. Bisphosphonates are subsequently released from the bone mineral during bone resorption, to be internalized by the activated osteoclasts [78,79]. Once taken up by an osteoclast, several biochemical processes involved in osteoclast function are disrupted (Fig. 3).

In general, all bisphosphonates inhibit osteoclast formation and migration, increase production of OPG by osteoblasts and promote osteoclast apoptosis [81,82]. Of note, bisphosphonates are rapidly removed from the blood stream via their avid binding to mineralized bone and via renal filtration of unbound drug [83]. As these agents do not readily cross the plasma membrane, the intracellular concentration of bisphosphonates in most tissues is very low. In clinical practice, four bisphosphonates (clodronate, pamidronate, ibandronate, and zoledronic acid) have been used to treat breast cancer patients with bone metastases. In a Cochrane review on placebo-controlled studies, the benefits of bisphosphonates to reduce SREs were clearly demonstrated [84]. The range of SRE risk reductions for bisphosphonates versus placebo were reported as 41% for intravenous zoledronic acid, 33% for intravenous pamidronate, and 18% for intravenous ibandronate. The SREs reduction with oral formulation of bisphosphonates was less impressive; with ibandronate producing 14% reduction of SREs compared to

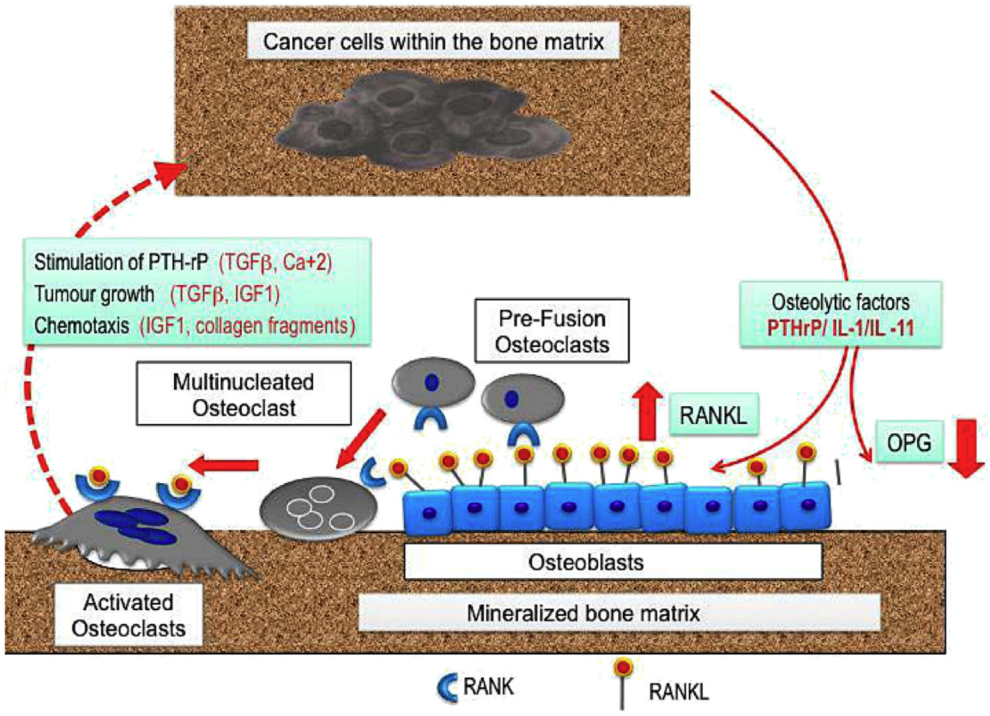

Fig. 2. Activation of osteoclasts (OC) and its interplay with breast cancer cells and bone microenvironment. PTHrP: parathyroid hormone related protein; TGFβ: transforming growth factor beta; Ca: calcium; IGF1: insulin growth factor 1; OPG: osteoprotegerin : RANKL: RANK ligand. Osteoclasts (OC) precursors differentiate from a population of monocytes (CFU-M), by virtue of their expression of the receptor RANK. RANKL – expressed by osteoblasts, and stromal cells – will bind to OC precursors with subsequent differentiation and fusion of these cells together to form multinucleated OCs and finally mature bone-resorbing OCs. Activated osteoclasts will then attach to the bone surface and via a proton pump mechanism it secrets hydrogen ions that dissolve bone minerals thus releasing calcium ions into the extracellular space. Osteoclasts also secret many proteolytic enzymes like matrix metalloproteinases, collagenases, to induce collagen degradation and digestion of the organic matrix. Large amount of TGF-b and IGF II and other cytokines stored in the mineralized bone matrix, will be released during OC bone resorption. When breast cancer cells colonize within the bone matrix, they start to secrete PTHrP and other osteolytic cytokines, which stimulate osteoblastic production of RANKL while reducing OPG levels, leading to enhanced bone resorption. Consequently the local milieu will be enriched by growth factors and other products of osteolysis (extracellular Ca++ and collagen fragments) which will induce: 1-stimulation of PTH-rP secretion (via TGF, Ca+ 2), 2-stimulation of tumor growth (via TGF, IGFII) and 3-chemotaxis of circulating tumor cells to arrest in bone matrix (via IGF I,collagen fragments). This evokes further PTHrP release with worsening osteolysis, in addition to supporting the growth of breast cancer cells within the bone matrix.
Adapted from: Azim & Azim, 2013

placebo ($p = 0.08$), whereas the oral clodronate studies suffered from lack of consistency, particularly with regard to improvement of bone pain [84] (Table 2).

In a phase III trial of bisphosphonates in patients with advanced breast cancer and osseous metastases or with multiple myeloma, 4 mg of zoledronic acid was compared to 90 mg pamidronate in reducing skeletal complications [89]. After 25 months of follow-up, zoledronic acid reduced the overall proportion of patients experiencing a second SRE by about one third compared with pamidronate, denoting the importance of maintaining these patients on a potent anti-resorption drug even after the development of a SRE [90]. The benefit was more evident among patients receiving endocrine therapy (30% reduction of skeletal complications; $p = 0.009$).

In patients with bone metastases and hypercalcemia, intravenous bisphosphonates in combination with saline rehydration ± corticosteriods therapy is the treatment of first choice [92–94].

In a pooled analysis of two randomized double-blind studies including 185 patients, zoledronic acid has shown a significant benefit in patients with hypercalcemia compared to pamidronate, in terms of complete response (82.6% versus 63.6%, respectively at day 7 of treatment ($p = 0.005$), and duration of response (30 days versus 17 days, respectively; $p = 0.001$) [95].

Other clinically relevant benefits of bisphosphonate treatment have been consistently reported, including significant pain relief, improved performance status and quality of life [84,96–100].

In spite of the considerable benefits of bisphosphonates in patients with bone metastases, a substantial proportion of the treated patients still suffer from repeated SREs and deterioration of bone pain as well as performance status. Hence, there is a clear need for improvement of what already has been achieved by these agents.

Denosumab

As previously mentioned, the imbalance in the RANKL/OPG ratio induced by bone metastases is considered as the main molecular event responsible for bone destruction. Therefore, targeting RANKL seems to be a very rational approach to treat bone metastases. Earlier attempts have tried to inhibit RANKL via increasing OPG levels. A genetically engineered recombinant OPG-Fc construct (AMGN-0007) was developed as a potential therapeutic agent for bone metastases, however, its use was associated with the formation of anti-AMGN-0007 antibodies, which precluded repeat administration of the drug. Furthermore, OPG is not specific to RANKL, as it can also block TRAIL [TNF related apoptosis inducing ligand], which is a principal mediator of tumor cell death induced by the host immune cells [101]. Therefore and as an alternative approach, an antibody specific to RANKL (Denosumab) was developed, which simulates the beneficial effects of OPG on bone health while avoiding any potential reaction with TRAIL [73]. Denosumab is a fully human monoclonal antibody that binds with a very high affinity and specificity to RANKL, with no detectable neutralizing antibodies in treated patients. Denosumab is able to inhibit

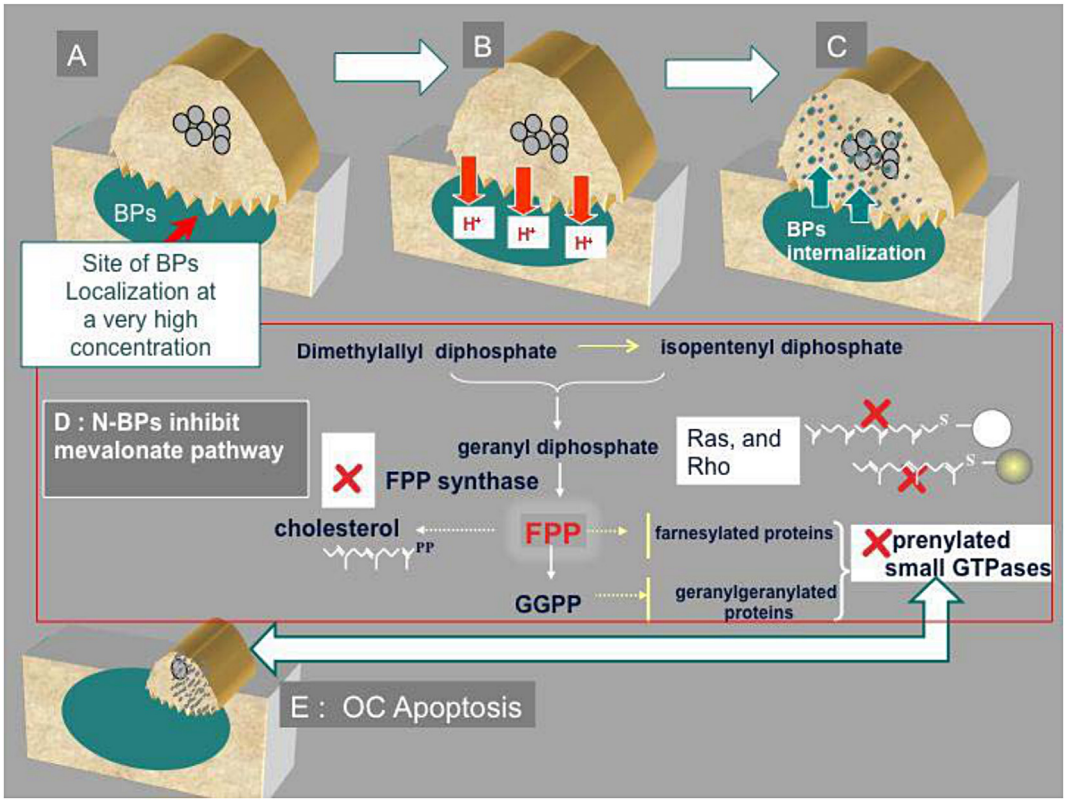

Fig. 3. Anti-osteoclastic and anti-tumor molecular mechanism of action of nitrogen-containing bisphosphonates. **A**: BPs localize with a very high affinity to skeletal areas of high bone turnover including osteolytic bone metastases where they are concentrated underneath the activated osteoclasts. **B**: BPs are subsequently released from the bone mineral during bone resorption, to be internalized by the activated osteoclasts. **C**: Within the osteoclasts (and also breast cancer cells) the N-BPs inhibit the activity of farnesyl diphosphonate (FPP) synthase, a key enzyme in the mevalonate pathway. FPP an enzyme necessary for prenylation of small guanine triphosphatases (GTPases)—such as Ras, Rac, and Rho, which are involved in intracellular signaling. D: Inhibition of the mevalonate pathway will ultimately cause osteoclasts to undergo apoptosis.
Adapted from: Azim et al., 2013

osteoclastic recruitment, maturation and function, with ultimate induction of apoptosis of the activated osteoclasts, and cessation of bone resorption [102].

Some mechanistic differences exist between the action of bisphosphonates and RANKL inhibitors (e.g. denosumab) in patients with bone metastases. In experimental models, bisphosphonates act only when taken up by the mature, actively resorbing osteoclasts, and thus residual osteoclasts can still be observed in bisphosphonate-treated bones. On the other hand, RANKL inhibitors block the activation, survival, and differentiation of osteoclasts from their precursors resulting in complete absence of osteoclasts in the treated bones (Fig. 4).

It should be emphasized that the therapeutic benefits of bisphosphonates and denosumab may not be restricted to their anti-resorptive effects in bone metastases. Accumulating evidence has shown that these agents may also exert – via different mechanisms – some potential anti-tumor effects in early breast cancer, which are beyond the scope of this manuscript [103–106].

The anti-osteoclastic promptness of RANKL inhibition over bisphosphonates, as shown in preclinical studies, was further confirmed by a randomized phase-II trial in patients with different solid tumors, mostly with prostate cancer [107]. All patients had elevated bone resorption markers (urinary NTx) despite ongoing bisphosphonate therapy. In this trial denosumab (180 mg either every 4 weeks or every 12 weeks) normalized uNTx levels significantly more frequently than the continuation of bisphosphonates. Fewer patients receiving denosumab (especially with the monthly dosing) experienced on-study SREs than those receiving intravenous bisphosphonates [107]. This study suggested a potential benefit of denosumab in patients lacking response to intravenous bisphosphonates.

A level one evidence of a clinically relevant superiority of denosumab over zoledronic acid has evolved from the results of three phase III studies of identical design, which included patients with bone metastases from breast cancer, prostate cancer, and other solid tumors (Table 3) [108–111]. In the breast cancer study ($n = 2046$), denosumab was significantly superior to zoledronic acid in delaying time to first on-study SRE (hazard ratio, 0.82; 95% CI, 0.71 to 0.95; $p = 0.01$) and time to first and subsequent (multiple) on-study SREs (rate ratio, 0.77; 95% CI, 0.66 to 0.89; $p = 0.001$) [109]. Denosumab was also superior to zoledronic acid in the reduction of the episodes of malignant hypercalcaemia ($p = 0.007$) [109].

An exploratory analysis for pain palliation and prevention has shown that the two drugs can provide similar beneficial effects in pain improvement (defined as ≥ 2 point decrease in worst pain score of brief pain inventory) as well as in median time to meaningful improvement of the worst pain score and the time to decreased pain interference [112]. In patients with no or mild pain (BPI Score 0–4) at baseline, denosumab significantly delayed pain worsening compared to zoledronic acid (295 days versus 176 days respectively; HR = 0.78 (95% CI: 0.67–0.92; $p = 0.0024$), with fewer denosumab-treated patients requiring strong opioid medications compared to zoledronic acid. [112]

This trial had a two-year open-label extension treatment phase in which the long-term safety profile of denosumab was confirmed

Table 2
Major clinical trials of intravenous bisphosphonates for SRE prevention in patients with breast cancer.

Study	Tumor type (*N*)	Therapy	Reduction of risk or rate of SREs[a]
Conte et al., 1996 [85]	BC ($N = 224$)	PAM vs. no PAM	↓ 20% (p = NA)
Hultborn et al., 1999 [86]	BC ($N = 404$)	PAM vs. placebo	↓ 30% ($p < 0.01$)
Lipton et al., 2000 [87]	BC ($N = 751$)	PAM vs. placebo	↓ 35% ($p < 0.001$)
Body et al., 2003 [88]	BC ($N = 462$)	IBN vs. placebo	↓ −18% ($p = 0.03$)
Rosen et al., 2001, 2003 [89,90]	BC, MM ($N = 1648$)	ZOL vs. PAM	↓ 20% ($p = 0.025$)
Kohno et al., 2005 [91]	BC ($N = 228$)	ZOL vs. placebo	↓ 41% ($p = 0.019$)

Abbreviations: BC, breast cancer; IBN, ibandronate; MM, multiple myeloma; NA, not available; PAM, pamidronate; SRE, skeletal-related event; ZOL, zoledronic acid.
[a] Ratio event rate bisphosphonate/control.

in patients who continued treatment with denosumab for up to 5 years or who switched from zoledronic acid to denosumab [113]. Overall survival over the entire study period was comparable with a median of 34.4 months (95% CI 31.5–39.3) for denosumab and 34.2 months (95% CI 31.0–37.6) for zoledronic acid.

Safety issues of bone-targeting therapies

The most common adverse effect encountered with intravenous bisphosphonates (zoledronic acid, ibandronate, and pamidronate) is **acute-phase reactions (APR)**, which occur in approx. 40% of the treated patients. However, the exact frequency and severity of AFR reported in clinical trials seem to vary markedly and comparison between these trials is difficult to interpret, because of differences in the definitions and methodologies used for reporting APR. Importantly, not all bisphosphonates induce APR to the same extent, with zoledronic acid apparently producing more APR than other bisphosphonates. Most evidence indicates that AFR is attributed to a transient release of pro-inflammatory cytokines (mostly TNF-α, IL-6, interferon γ) from γ δ T-lymphocytes, which are activated in response to bisphosphonates [114–116]. The clinical presentation comprises fever, chills, myalgia, arthralgia, nausea, vomiting and bone pain that occur typically after the initial infusions. These flu-like symptoms are, generally mild, self-limited and usually resolve over 3 days. APR respond well to nonsteroidal anti-inflammatory drugs and antipyretic agents such as paracetamol or acetaminophen [117]. Although not life-threatening and not precluding subsequent bisphosphonate treatment, APR is often perceived by the patient as a stressful condition that occasionally may be severe and lead to treatment withdrawal. Hence, prior to treatment with bisphosphonates, the patients should be informed about the manifestations of APR and pretreated accordingly.

The mechanism of action of denosumab does not entail similar immunostimulatory reactions, and therefore, its use is not associated with release of pro-inflammatory cytokines. Accordingly, denosumab treatment is not expected to induce any clinically relevant APR. A pooled analysis of adverse events in the clinical trials investigating efficacy and safety of denosumab found a significantly lower incidence of these reactions with denosumab compared to zoledronic acid (8% versus 20%, respectively) [118].

Although this difference is clinically meaningful, the occurrence of APR in denosumab treated patients is still not fully explained. This data may reflect the inherent difficulty to report about the components of APR in a population of patients who have a widespread cancer, receive a multitude of medications, and in whom fever, arthralgia, nausea, vomiting and skeletal pains can also occur for other reasons. No cases of APR have been reported with denosumab in a huge data set of osteoporosis studies.

APR should not be mixed up with a chronic form of musculoskeletal pain that is also associated with bisphosphonates use. An FDA alert [1/7/2008] has highlighted the possibility of severe and sometimes incapacitating bone, joint, and/or muscle pain in bisphosphonate-treated patients that may occur within days, months, or years after starting a bisphosphonate. Although this notion is included in the prescribing information for all bisphosphonates, this form of musculoskeletal pain may be overlooked by healthcare professionals. Some patients have reported complete relief of symptoms after discontinuing the

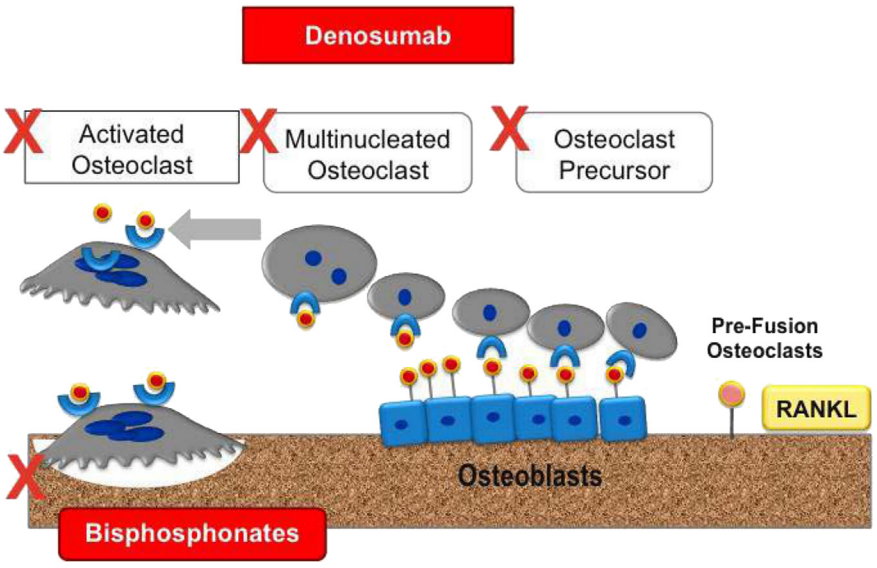

Fig. 4. Mechanistic differences between the anti-osteoclastic action of RANKL inhibition (denosumab) and bisphosphonate. BPs act only when taken up by the mature, actively resorbing osteoclasts, and thus residual osteoclasts can still be observed in bisphosphonate-treated bones. On the other hand, RANKL inhibitors block the activation, survival, and differentiation of osteoclasts from their precursors resulting in complete absence of osteoclasts in the treated bones. Adapted from: Azim et al., 2013.

Table 3
Three identically designed phase III clinical trials of denosumab (120 mg s.c. q4 weeks) vs. zoledronic acid (4 mg iv q4 weeks) in patients with breast cancer/prostate cancer/other solid tumors or myeloma and at least one skeletal metastasis.

Author	Patients (n) (denosumab vs. zoledronic acid)	Patient Population	Results
Stopeck et al., 2010 [109]	1026 vs 1020	Breast cancer	Delayed time to first on-study SRE (HR 0.82, $p < 0.0001$ non- inferiority, $p = 0.001$ superiority) Delayed time to first and subsequent on-study SRE (rate ratio 0.77, $p = 0.001$)
Fizazi et al., 2011 [108]	951 vs. 950	Castration resistant prostate cancer	Delayed time to first on-study SRE (HR 0.82, $p < 0.0002$ for non- inferiority, $p = 0.008$ superiority) Delayed time to first and subsequent on-study SRE (rate ratio 0.82, $p = 0.008$)
Henry et al., 2011 [111]	886 vs. 890	NSCLC, SCLC, renal, myeloma, other	Delayed time to first on-study SRE (HR 0.84, $p < 0.0007$ for non- inferiority; NS ($p = 0.03$)for superiority; No difference in time to first and subsequent on-study SRE (rate ratio 0.90, $p = 0.14$)

bisphosphonate, whereas others have reported slow or incomplete resolution. The pathophysiology of this type of musculoskeletal pain is still unknown.

In general, all bisphosphonates can induce **renal tubular damage**, but there are considerable differences between the individual drugs to cause such a potential damage. Following administration, bisphosphonates are eliminated through the kidney by filtration and active secretion [119]. Influx of these drugs into the renal tubular cells is passive and depends only on serum concentration and protein binding in addition to renal tissue half-life. An active, albeit limited transportation mechanism forms the basis for their excretion into the lumen. If this mechanism is overloaded (e.g. higher than standard doses or with rapid intravenous infusion) [120]. Bisphosphonates will accumulate in the tubular cells, resulting in cellular damage and renal impairment.

The renal tissue half-life is especially high with zoledronic acid (150–200 days) compared to ibandronate (24 days), which could explain the cumulative renal toxicity of the former compound [108]. According to the prescribing information, zoledronic acid and pamidronate are not recommended in patients with severe renal impairment (serum creatinine > 3 mg/dl or creatinine clearance < 30 ml/min) [121]. This does not apply to ibandronate, which can be administered at a reduced dose in patients with CrCl < 30 ml/min [122].

To ensure safety, monitoring of serum creatinine levels before each bisphosphonate infusion and subsequent dosing and/or infusion rate adjustments are recommended [119,123]. Further preventive measures include adequate hydration and avoiding concurrent nephrotoxic agents (e.g. non-steroidal inflammatory drugs, radiographic contrast dye). If these agents must be applied in patients treated with zoledronic acid, they should be administered at least 24 h after the zoledronic acid infusion [124].

Although renal toxicity has been reported with denosumab, it was significantly less common than with zoledronic acid in the breast cancer study (4.9% vs 8.5%, respectively; $p = 0.001$) [109]. Unlike bisphosphonates, denosumab is not excreted via the kidneys, and has been consistently acknowledged as safe to use in chronic kidney disease (CKD). In general, denosumab does not require renal monitoring or dose adjustment even in patients with renal impairment [125,126]. Relatively small number of patients with CKD stage 3 and 4 were enrolled in denosumab pivotal trials. However, a special warning should be made for patients with bony metastases and CKD stage 4 and 5, a population with renal osteodystrophy who are much more prone to develop severe potentially fatal hypocalcemia in response to denosumab.

Hypocalcemia can occur with both bisphosphonates and denosumab due to their potent inhibition of the process of bone resorption including suppression of calcium ion release. Patients with pre-existing hypocalcemia and patients with severe renal insufficiency are especially susceptible to develop severe symptomatic hypocalcemia, hence this electrolyte imbalance should be corrected prior to initiation of bone-targeting therapies and regular monitoring of calcium levels is recommended throughout the treatment period [127]. Furthermore, daily calcium intake and vitamin D supplementation is highly recommended during treatment with all bone-targeting therapies. In the integrated analysis of the three pivotal trials, the incidence of hypocalcemia was significantly higher in patients treated with denosumab (9.6% compared to zoledronic acid 5%) [128,129].

Osteonecrosis of the jaw (ONJ) is an uncommon albeit potentially long-lasting and serious adverse event of bisphosphonates and denosumab [109,118,129,130].

In a reported pivotal phase III trial ONJ occurred infrequently after 2–3 years of treatment (2.0%, denosumab; 1.4%, zoledronic acid; $p = 0.39$) with a cumulative incidence of 4.7% for denosumab patients and 3.5% for zoledronic acid patients for the entire study duration of 5 years [113].

In prospective clinical trials and retrospective data analyses several risk factors for the development of ONJ have been identified such as longer treatment and higher cumulative doses of intravenous bisphosphonate therapy, poor oral health, and dental extractions [130,131]. Additional risk factors include concurrent administration of certain chemotherapeutic agents, anti-angiogenic drugs or corticosteroids given for a prolonged period of time [132].

Preventive dental measures include a pre-therapy dental assessment, periodical dental examinations, and limitation of invasive dental procedures while on treatment. Furthermore, patients should be encouraged to proactively follow a thorough and consistent oral hygiene routine to reduce the risk of infection and ONJ. In several studies these preventive measures have proven to significantly reduce the annual incidence of ONJ in patients treated with bisphosphonates [131–134].

Guidelines for the treatment of bone metastases from breast cancer

Current international guidelines for prevention of SRE recommend the use of denosumab or intravenous bisphosphonates such as ibandronate, pamidronate and zoledronic acid, which are approved for the prevention of SRE in patients with advanced breast cancer and bone metastases. Most guidelines suggest that, given the potential of bone-modifying agents to delay time to first SRE, these agents should be started when bone metastases are diagnosed, even when patients are asymptomatic.

While the ASCO guidelines recommend initiating treatment with bisphosphonates or denosumab only for patients with evidence of bone destruction due to bone metastases [135], other guidelines recommend treatment with these agents in the presence of bone metastases confirmed by X-ray, CT or MRI without further specifications [136–138]. All the available guidelines and expert panels do recommend treatment to be continued

indefinitely until the patient's performance status is substantially decreased. Indeed, most patients will remain on these agents "on a monthly basis throughout patients' lifetime". Of note, all of these guidelines have been recommended in the absence of convincing data from clinical trials for optimal use of bone-modifying agents, mainly in regard to initiation and treatment duration.

The components of the most recent versions of these guidelines are outlined in Table 4.

Expert panel recommendations for clinical practice

Radiation therapy

The single-fraction treatment approach has been clearly shown to provide equal efficacy in terms of pain control with similar or probably less acute toxicity. Moreover, it is more economical and convenient to patients and caregivers [139]. Nevertheless, and despite numerous randomized trials, meta-analyses and guidelines, which recommend against multi-fraction regimens, the literature survey has shown that the 10-fraction regimen continues to be the preferred treatment adapted by the majority of radiation oncologists. We strongly encourage to adapt the single dose fraction for uncomplicated painful bone metastases without pathological fractures or spinal cord compression, especially in patients with dominant visceral disease or with a life expectancy of less than 6 months.

Solitary bone metastases

The concept of oligometastasis, introduced by Hellman and Weichselbaum in 1995, implied that local treatments such as surgery or radiation therapy are potentially curative in a proportion of patients with metastases [140]. Oligometastases have long been considered a rare exception, but are becoming more frequently identified with highly sensitive radiological procedures for their detection [141].

Solitary metastatic disease should be confirmed by biopsy whenever possible since some benign osseous conditions can be difficult to distinguish from metastasis solely by imaging.

For single bone lesions surgery is a viable option. Surgical procedures are guided by anatomical site of the lesion. More aggressive treatment may be beneficial in patients with a higher expected survival rate.

If the lesion is in the cervical spine, prophylactic radiation should also be considered since a fracture in this segment of the spine is very difficult to treat.

More recently, single osseous lesions have also been the focus of studies with different SBRT schedules [142]. Several non-randomized studies have shown that SBRT for single lesions is a safe and effective treatment option with high local tumor control rates of about 80% [143]. However, larger randomized controlled studies with longer follow-up are required to determine the curative potential of SBRT.

Currently evidence from clinical trials is lacking to recommend one treatment approach over the other.

Evaluation of response to treatment

For the assessment of response to treatment in skeletal sites no universally accepted single method exists, thus response is commonly assessed by a combination of symptom evaluation, imaging tests and biochemical markers. Biochemical markers of bone turnover such as collagen type I telopeptides (NTX and CTX) have shown promising results in correlative studies, but they are not widely used in clinical practice due to their lack of sensitivity and specificity [129,144].

In an observational study of patients with prostate cancer, patients with the highest baseline levels had also the worst prognosis, although there was no correlation between biomarker levels and disease progression [145].

Accurate assessment of response to treatment in bone metastases requires visualizing not only the tumor burden but also the structural changes in the bone. All of the commonly used imaging modalities (plain radiography, skeletal scintigraphy, MRI, PET) have their advantages and disadvantages: with plain radiography, it may take 3–6 months and more than 30–50% of mineral loss might occur before changes become visible. Moreover, it can only depict changes in bone structure, but not changes in the tumor itself. With skeletal scintigraphy, which reflects bone blastic activity, it can also take 6 months or longer to reliably detect a response because of the confounding phenomenon of a treatment-induced healing flare, a spurious increase in radionuclide uptake, which occurs due to the reparative mineralization around healing metastases [146,147].

With CT scans both structural changes in the bone and anatomic changes associated with the target tumor can be depicted. MRI can optimally show spinal cord status and changes in the bone marrow, but it is not useful to show lytic or blastic changes in bone structure.

PET/CT is recognized as an appealing functional tool in assessing response to therapy because it is sensitive to the metabolic changes in the tumor mass that not only precede morphological changes but

Table 4
Indications and guidance for treatment of bone metastases in breast cancer with bone-targeted therapies in current guidelines.

ASCO 2011[136]	NCCN V.2.2013[137]	ESMO 2012[138]	ABC-1 2012[139]
Women with evidence of bone destruction on plain radiographs/CT/MRI	Presence of bone metastases as confirmed by imaging (X-ray, CT or MRI)	Hypercalcaemia and clinically evident bone metastases	Presence of bone metastases
Bone scan alone provides not enough evidence	Expected survival ≥3 mo and renal function adequate		Optimal timing and duration of treatment with bone modifying agent is less clear in case of an isolated bone lesion
Denosumab 120 mg sc every 4 weeks	Zoledronic acid may be superior to pamidronate in lytic metatases	Bisphosphonates	Bisphosphonate or denosmab in combination with other systemic agents
Pamidronate 90 mg iv 2 h Q every 3–4	Zoledronic acid 4 mg iv 15 min every 3–5 weeks	Recent studies showed superior activity and favorable toxicity profile of denosumab in breast cancer	
Weeks	Pamidronate 90 mg iv 90 min every 3–5 weeks	Choice of drugs, timing, optimal duration, methods of administration and side effects should be considered individually	
Zoledronic acid 4 mg iv 15 min every 3–4 weeks	Calcium (1200–1500 mg/day)		
Insufficient evidence supporting efficacy of one bisphosphonate over the other	Vitamin D (400–800 IU/day)		

also precede changes in markers of tumor viability. PET/CT is considered as one of the most encouraging diagnostic tools in the emerging field of theranostics, which hold promise of increasing the efficiency and effectiveness of cancer care [148].

18F-fluoride PET is being used for evaluation of blastic metastases, but widespread use is limited. Improved imaging techniques such as WBD-MRI in combination with anatomic imaging may be able to identify patients who are responding to therapy at very early stages – even prior to gross morphological changes – based on cellularity through both qualitative and quantitative assessments rendering this a promising tool in the verification of response to therapies aimed at metastatic bone disease [19].

Choice of bone-targeted agent

While we certainly acknowledge the fact that all of the approved bone-modifying agents are able to provide a significant benefit to the patients in terms of prevention of SREs and reduction of bone pain, we can't agree with the ASCO statement that there is "insufficient evidence to demonstrate greater efficacy of one bone-modifying agent over another" [135]. As mentioned earlier, head-to-head comparative phase III trials have shown a significant superiority of zoledronic acid over pamidronate in multiple event analysis, and a significant advantage of denosumab compared to zoledronic acid in the reduction of SRE as well as multiple event analysis. When considering an adequate long-term treatment in a given patient, other issues beyond efficacy should also be taken into account such as tolerability and safety, especially in the presence of comorbidities, in addition to convenience and time of treatment administration. All of these factors would favor the use of denosumab in breast cancer patients with bone metastases over zoledronic acid and other bisphosphonates. Denosumab did not improve progression free survival, disease free survival or overall survival in either one of the phase III trials mentioned.

However, in many institutions, selection of bone-modifying agents will also be influenced by other factors like treatment availability and costs. Denosumab is not universally registered and/or reimbursed and its costs is markedly higher than the costs of bisphosphonates.

Regardless of which agent is used, the available guidelines and expert panels do recommend treatment to be continued indefinitely until the patient's performance status is substantially decreased. Indeed, most patients will remain on these agents "on monthly basis for life long" [120,149].

Whenever a SRE occurs while on treatment, the consensus is never to stop treatment with the bone-modifying agents, as this treatment is still able to reduce subsequent SREs. In fact, the risk of subsequent SREs increases after the first SRE which will have negative consequences for patients' functional independence, as well as overall survival especially in patients with fractures. The idea of switching to a more potent bisphosphonate or to denosumab may be clinically plausible, with some small clinical studies suggesting improved response with this approach [107,150,151].

In one study, which prospectively evaluated radiological changes assessed by thoraco-lumbar CT, switching from early generation bisphosphonates to the more potent zoledronic acid was associated with a significant increase in bone density and in osteoblastic volume in the vertebrae [152]. Also, the data on denosumab's ability to significantly suppress bone resorption markers in patients with elevated markers despite intravenous bisphosphonates, may also suggest that shifting to a more potent agent might be potentially advantageous. However, it is not yet clear, whether this approach will be able to actually reduce SREs significantly, which is the primary objective of this class of agents.

Dose frequency

The recommended dose and schedule of bone-modifying agents therapy have been established in registration trials. Nevertheless, one of the most frequently asked questions is whether we may shift to a more protracted dose schedule (e.g. 12 weeks), after an initial phase of the standard monthly regimen, as this may contribute to improved safety and reduced cost. The issue may be specifically relevant in non-symptomatic patients with ongoing disease response. This question was addressed by a recent phase III study – the ZOOM trial – in which patients ($n = 425$) who finished 9–12 monthly treatment with zoledronic acid, were further randomized to receive the drug on a monthly or quarterly basis. The skeletal morbidity rate (SMR; number of SREs/patient/year) was the primary endpoint, and it was similar in both arms, with likewise no significant difference in the toxicity profile. The authors reported that bone resorption markers were significantly more suppressed with the monthly regimen and concluded that further follow-up is needed for a final answer [153].

The results of several other trials are awaited and should provide further information of the treatment outcome with reduced frequency zoledronate. OPTIMIZE-2 is an ongoing trial with patient population and design similar to ZOOM trial. In the BISMARK trial, patients are randomized to either standard schedule of zoledronic acid or to resorption marker-directed regimen. Reported data suggest that zoledronate every three to four weeks may be necessary when bone resorption markers (urinary N-terminal telopeptide) are increased [154].

CALGB 70604 is a large randomized phase 3 trial of standard vs prolonged dosing interval of zolendronate in patients with breast cancer, prostate cancer and multiple myeloma. The accrual has been completed.

Untill more data are available, we prefer to treat all patients according to the label indications of the registered bone-targeted therapies.

Data on frequency of administration available for denosumab is limited. In a phase II study suppression of uNTx as primary end point was sustained through 12 weeks in patients dosed every 4 weeks with denosumab, but the same did not happen in patients treated with the every 12 weeks dosing schedule. Evidence of escape from suppression was observed at week 13 [155]. In a similar Japanese phase I study also a trend to superior efficacy of denosumab every 4 weeks was seen [156].

A special situation may be in patients with oligo-/solitary bone metastases whose disease may be in a perfect control by SBRT. For these cases the ABC guidelines stated that "Optimal timing and duration of treatment with bone-modifying agent is less clear in case of an isolated bone lesion". Having the preliminary results of the ZOOM study may be a good rational to discuss the merits of the monthly versus the 3 monthly schedule with those patients.

In case of a complete radiographic remission and irrespective to the agent used and the schedule adapted the expert panel recommends not to stop treatment.

Management of ONJ

For patients who are on intravenous bisphosphonate therapy and require dental procedures there is a suggestion that prophylactic antibiotic use prior and after the procedure is performed might be helpful in reducing ONJ risk [157]. If a surgical procedure is necessary, bone-targeted agents may be stopped and restarted after healing. However, there is insufficient evidence that a "drug holiday" may prevent ONJ [158]. Moreover, because of their long half-life any effect of stopping bisphosphonates on the risk of developing ONJ is unlikely [159].

If a patient develops ONJ, current recommendations are to treat ONJ conservatively and avoid additional invasive surgeries [149,160]. There is no evidence that discontinuing bone-targeted therapy improves the outcome of ONJ [158,161].

In a combined analysis of three trials with denosumab and zoledronic acid, ONJ occurred infrequently (89 patients of 5723, 1.6%) [162]. Resolution of ONJ occurred in 36.0% (32 of 89) of patients. 25 (78.1%) of these patients discontinued treatment, while 7 (21.9%) received at least one active dose of drug after diagnosis of ONJ. As all patients with ONJ stopped treatment for a period of time, this analysis is unable to shed further light on this issue [162].

Therefore, any decisions concerning any change in bisphosphonate or denosumab treatment should be based on a balanced risk-benefit assessment for each individual patient.

Conclusions

Bone metastases are extremely common in patients with advanced breast cancer. Due to their propensity to cause severe symptoms and incapacitating complications, they add a lot to the already compromised patient's quality of life. In the vast majority of patients, treatment of bone metastasis is palliative, and the goals are to relieve pain, maintain skeletal integrity, improve function, and prevent SRE. Ideally, a multidisciplinary approach is required in order to tailor the treatment strategy according to the specific clinical scenario in each patient. The different treatment options should be discussed with the patient and carefully considered to give the best palliative care while minimizing potential side effects.

Bisphosphonates have an established role in the treatment of bone metastases, with zoledronic acid apparently producing the most convincing efficacy data in breast cancer as well as in other solid tumors. Recently, denosumab has been added to the therapeutic armamentarium and has shown a significant superiority compared to zoledronic acid, both in the prevention of SREs and in delaying of significant pain. These two clinically relevant advantages of denosumab over zoledronic acid, would strongly suggest the need for a wider patients' accessibility to this new drug.

The optimal use of these agents in breast cancer patients with bone metastases still requires further fine-tuning, which awaits answers from clinical trials – such as what is the role of bone turnover markers to identify low- and high-risk patients for SREs? Is there a possibility of less frequent administration of bone-targeted agents? More research is required to answer these questions and thereby enhancing the evidence base guiding current treatment strategies. Finally, new osteoclast inhibitors are currently under investigation, and these agents may offer further therapeutic benefit for patients with bone metastases.

Conflict of interest statement

Dr. Hamdy Azim, Speaker, Novartis and Amgen. The other authors have no conflict of interest.

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The authors take full responsibility for the content of this publication and confirm that it reflects their viewpoint and medical expertise.

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References

[1] Van Poznak C. Predicting skeletal complications in metastatic breast cancer raises challenges. Breast Cancer Res Treat 2010;123:781–3.
[2] Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer 2007;110:1860–7.
[3] Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 2008;19:420–32.
[4] Hadji P, Aapro MS, Body JJ, Bundred NJ, Brufsky A, Coleman RE, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. Ann Oncol 2011;22:2546–55.
[5] Rybak LD, Rosenthal DI. Radiological imaging for the diagnosis of bone metastases. Q J Nucl Med 2001;45:53–64.
[6] Gold RI, Seeger LL, Bassett LW, Steckel RJ. An integrated approach to the evaluation of metastatic bone disease. Radiol Clin North Am 1990;28:471–83.
[7] Kattapuram SV, Khurana JS, Scott JA, El–Khoury GY. Negative scintigraphy with positive magnetic resonance imaging in bone metastases. Skelet Radiol 1990;19:113–6.
[8] Gonzalez–Sistal A, Baltasar Sanchez A, Herranz Carnero M, Ruibal Morell A. Advances in medical imaging applied to bone metastases. In: Erondu OE, editor. Medical imaging. InTech; 2011, ISBN 978-953-307-774-1. Available from: http://www.intechopen.com/books/medicalimaging/advances-in-medical-imaging-applied-to-bone-metastases.
[9] Choi J, Raghavan M. Diagnostic imaging and image–guided therapy of skeletal metastases. Cancer Control 2012;19:102–12.
[10] Sequeiros RB, Fritz J, Ojala R, Carrino JA. Percutaneous magnetic resonance imaging-guided bone tumor management and magnetic resonance imaging-guided bone therapy. Top Magn Reson Imaging 2011;22:171–7.
[11] Peterson JJ, Kransdorf MJ, O'Connor MI. Diagnosis of occult bone metastases: positron emission tomography. Clin Orthop Relat Res 2003;(415 Suppl.):S120–8.
[12] Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with 18Fluoride: applying new technology to an old tracer. J Nucl Med 2008;49(1):68–78.
[13] Cook GJ, Fogelman I. The role of positron emission tomography in skeletal disease. Semin Nucl Med 2001;31(1):50–61.
[14] Rong J, Wang S, Ding Q, Yun M, Zheng Z, Ye S. Comparison of 18 FDG PET-CT and bone scintigraphy for detection of bone metastases in breast cancer patients. A meta-analysis. Surg Oncol 2013;22:86–91.
[15] Shie P, Cardarelli R, Brandon D, Erdman W, Abdulrahim N. Meta-analysis: comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. Clin Nucl Med 2008;33:97–101.
[16] Groheux D, Giacchetti S, Moretti JL, Porcher R, Espié M, Lehmann-Che J, et al. Correlation of high 18F-FDG uptake to clinical, pathological and biological prognostic factors in breast cancer. Eur J Nucl Med Mol Imaging 2011;38:426–35.
[17] Montgomery SK, Barlow WE, Linden HM, Gralow JR, Ellis GK, Gadi VK et al. Serial FDG and 18 F-fluoride PET predict reponse to therapy in patients with breast cancer bone metastases. Poster No. P4-01-01 presented at the San Antonio Breast Cancer Symposium (SABCS), December 10–14, 2013.
[18] Baur-Melnyk A. Malignant versus benign vertebral collapse: are new imaging techniques useful? Cancer Imaging 2009;9(Spec No A):S49–51.
[19] Li SP, Padhani AR. Tumor response assessments with diffusion and perfusion MRI. J Magn Reson Imaging 2012;35(4):745–63.
[20] Baur A, Stäbler A, Brüning R, Bartl R, Krödel A, Reiser M, et al. Diffusion–weighted MR imaging of bone marrow: differentiation of benign versus pathologic compression fractures. Radiology 1998;207(2):349–56.
[21] Karchevsky M, Babb JS, Schweitzer ME. Can diffusion-weighted imaging be used to differentiate benign from pathologic fractures? A meta-analysis. Skelet Radiol 2008;37(9):791–5.
[22] Mubarak F, Akhtar W. Acute vertebral compression fracture: differentiation of malignant and benign causes by diffusion weighted magnetic resonance imaging. J Pak Med Assoc 2011;61(6):555–8.
[23] Wu JS, Wong R, Johnston M, Bezjak A, Whelan T, Cancer Care Ontario Practice Guidelines Initiative Supportive Care Group. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. Int J Radiat Oncol Biol Phys 2003;55(3):594–605.
[24] Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy – a systematic review of the randomised trials. Cochrane Database Syst Rev 2004;(2):CD004721.
[25] Falkmer U, Jarhult J, Wersall P, Cavallin-Stahl E. A systematic overview of radiation therapy effects in skeletal metastases. Acta Oncol 2003;8:620–33.
[26] Napoli A, Anzidei M, Marincola BC, Brachetti G, Noce V, Boni F, et al. MR imaging-guided focused ultrasound for treatment of bone metastasis. Radiographics 2013;33(6):1555–68.
[27] Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. Radiother Oncol 1999;52(2):101–9.
[28] Roos DE, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH, , et alTrans-Tasman Radiation Oncology Group, TROG 96.05. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). Radiother Oncol 2005;75(1):54–63.

[29] Foro Arnalot P, Fontanals AV, Galcerán JC, Lynd F, Latiesas XS, de Dios NR, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiother Oncol 2008;89(2):150–5.

[30] Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol R Coll Radiol 2012;24(2):112–24.

[31] Koswig S, Budach V. Remineralization and pain relief in bone metastases after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study. Strahlenther Onkol 1999;175(10):500–8.

[32] Mithal N, Needham P, Hoskin P. Retreatment with radiotherapy for painful bone metastases. Int J Radiat Oncol Biol Phys 1994;29:1011–4.

[33] Jeremic B, Shibamoto Y, Igrutinovic I. Single 4 Gy re-irradiation for painful bone metastases following single fraction radiotherapy. Radiother Oncol 1999;52(2):123–7.

[34] Lo SS, Sahgal A, Wang JZ, Mayr NA, Sloan A, Mendel E, et al. Stereotactic body radiation therapy for spinal metastases. Discov Med 2010;9(47):289–96.

[35] Sohn S, Chung CK. The role of stereotactic radiosurgery in metastasis to the spine. J Korean Neurosurg Soc 2012;51(1):1–7.

[36] Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach 3rd M, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 2005;97:798–804.

[37] Chow E, Ling A, Davis L, Panzarella T, Danjoux C. Pain flare following external beam radiotherapy and meaningful change in pain scores in the treatment of bone metastases. Radiother Oncol 2005;75:64–9.

[38] Loblaw DA, Wu JS, Kirkbride P, Panzarella T, Smith K, Aslanidis J, et al. Pain flare in patients with bone metastases after palliative radiotherapy – a nested randomized control trial. Support Care Cancer 2007;15:451–5.

[39] Hird A, Zhang L, Holt T, Fairchild A, DeAngelis C, Loblaw A, et al. Dexamethasone for the prophylaxis of radiation-induced pain flare after palliative radiotherapy for symptomatic bone metastases: a phase II study. Clin Oncol R Coll Radiol 2009;21(4):329–35.

[40] Rose PS, Laufer I, Boland PJ, Hanover A, Bilsky MH, Yamada J, et al. Risk of fracture after single fraction image-guided intensity-modulated radiation therapy to spinal metastases. J Clin Oncol 2009;27(30):5075–9.

[41] Cunha MV, Al-Omair A, Atenafu EG, Masucci GL, Letourneau D, Korol R, et al. Vertebral compression fracture (VCF) after spine stereotactic body radiation therapy (SBRT): analysis of predictive factors. Int J Radiat Oncol Biol Phys 2012;84(3):e343–9.

[42] Rodríguez-Ruiz ME, San Miguel I, Gil-Bazo I, Perez-Gracia JL, Arbea L, Moreno-Jimenez M, et al. Pathological vertebral fracture after stereotactic body radiation therapy for lung metastases. Case report and literature review. Radiat Oncol 2012;7:50.

[43] Boehling NS, Grosshans DR, Allen PK, McAleer MF, Burton AW, Azeem S, et al. Vertebral compression fracture risk after stereotactic body radiotherapy for spinal metastases. J Neurosurg Spine 2012;16(4):379–86.

[44] Malawer M, Sugarbaker PH. Musculoskeletal cancer surgery. Treatment of sarcomas and allied diseases. New York: Kluwer Academic Publishers; 2004.

[45] Bartels RH, van der Linden YM, van der Graaf WT. Spinal extradural metastasis: review of current treatment options. CA Cancer J Clin 2008;58(4):245–59.

[46] Klimo Jr P, Thompson CJ, Kestle JR, Schmidt MH. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. Neuro Oncol 2005;7(1):64–76.

[47] Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 2005;366(9486):643–8.

[48] Chi JH, Gokaslan Z, McCormick P, Tibbs PA, Kryscio RJ, Patchell RA. Selecting treatment for patients with malignant epidural spinal cord compression-does age matter?: results from a randomized clinical trial. Spine (Phila Pa 1976;2009(34):431–5.

[49] Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosis of impending pathological fractures. Clin Orthop 1989;249:256–64.

[50] Damron TA, Morgan H, Prakash D, Grant W, Aronowitz J, Heiner J. Critical evaluation of Mirels' rating system for impending pathologic fractures. Clin Orthop Relat Res 2003;(415 Suppl.):S201–7.

[51] Mac Niocaill RF, Quinlan JF, Stapleton RD, Hurson B, Dudeney S, O'Toole GC. Inter- and intra-observer variability associated with the use of the Mirels' scoring system for metastatic bone lesions. Int Orthop 2011;35(1):83–6.

[52] Rades D. Dose-fractionation schedules for radiotherapy of bone metastases. Breast Care (Basel) 2010;5(5):339–44.

[53] Eastley N, Newey M, Ashford RU. Skeletal metastases – the role of the orthopaedic and spinal surgeon. Surg Oncol 2012;21(3):216–22.

[54] Hirsch AE, Jha RM, Yoo AJ, Saxena A, Ozonoff A, Growney MJ, et al. The use of vertebral augmentation and external beam radiation therapy in the multimodal management of malignant vertebral compression fractures. Pain Physician 2011;14(5):447–58.

[55] Chwistek M, Mehta RS. Vertebroplasty and kyphoplasty for vertebral compression fractures #202. J Palliat Med 2012;15(10):1151–2.

[56] Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. Eur Spine J 2007;16(8):1085–100.

[57] Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med 2009;361:557–68.

[58] Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569–79.

[59] Wardlaw D, Cummings SR, Van Meirhaeghe J, Bastian L, Tillman JB, Ranstam J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet 2009;373(9668):1016–24.

[60] Klazen CA, Lohle PN, de Vries J, Jansen FH, Tielbeek AV, Blonk MC, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. Lancet 2010;376:1085–92.

[61] Papanastassiou ID, Phillips FM, Van Meirhaeghe J, Berenson JR, Andersson GB, Chung G, et al. Comparing effects of kyphoplasty, vertebroplasty, and non-surgical management in a systematic review of randomized and non-randomized controlled studies. Eur Spine J 2012;21(9):1826–43.

[62] Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, , et alCancer Patient Fracture Evaluation (CAFE) Investigators. Balloon kyphoplasty versus non–surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 2011;12(3):225–35.

[63] Tomblyn M. The role of bone–seeking radionuclides in the palliative treatment of patients with painful osteoblastic skeletal metastases. Cancer Control 2012;19(2):137–44.

[64] Christensen MH, Petersen LJ. Radionuclide treatment of painful bone metastases in patients with breast cancer: a systematic review. Cancer Treat Rev 2012;38(2):164–71.

[65] Resche I, Chatal JF, Pecking A, Ell P, Duchesne G, Rubens R, et al. A dose-controlled study of 153Sm ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases. Eur J Cancer 1997;33(10):1583–91.

[66] Sciuto R, Festa A, Pasqualoni R, Semprebene A, Rea S, Bergomi S, et al. Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients. Breast Cancer Res Treat 2001;66(2):101–9.

[67] Baczyk M, Czepczyński R, Milecki P, Pisarek M, Oleksa R, Sowiński J. 89Sr versus 153Sm–EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. Nucl Med Commun 2007;28(4):245–50.

[68] Rasulova N, Lyubshin V, Arybzhanov D, Krylov V, Khodjibekov M. Effectiveness of bone metastases treatment by sm-153 oxabifore in combination with monoclonal antibody denosumab (xgeva): first experience. World J Nucl Med 2013;12(1):19–23.

[69] Boyce BF, Rosenberg E, de Papp AE, Duong le T. The osteoclast, bone remodelling and treatment of metabolic bone disease. Eur J Clin Invest 2012;42(12):1332–41.

[70] Khosla S. Minireview: the OPG/RANKL/RANK system. Endocrinology 2001;142:5050–5.

[71] Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 2003;423:337–42.

[72] Li J, Sarosi I, Yan XQ, Morony S, Capparelli C, Tan HL, et al. RANK is the intrinsic hematopoietic cell surface receptor that controls osteoclastogenesis and regulation of bone mass and calcium metabolism. Proc Natl Acad Sci USA 2000;97(4):1566–71.

[73] Azim HA, Kamal NS, Azim Jr HA. Bone metastasis in breast cancer: the story of RANK ligand. J Egypt Natl Canc Inst 2012;24(3):107–14.

[74] Chappard D, Bouvard B, Baslé MF, Legrand E, Audran M. Bone metastasis: histological changes and pathophysiological mechanisms in osteolytic or osteosclerotic localizations. A review. Morphologie 2011;95(309):65–75.

[75] Hofbauer LC, Schoppet M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 2004;292(4):490–5.

[76] Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27(3):165–76.

[77] Hadji P. Clinical considerations for the use of antiresorptive agents in the treatment of metastatic bone disease. Crit Rev Oncol Hematol 2011;80(2):301–13.

[78] Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J, et al. Cellular and molecular mechanisms of action of bisphosphonates. Cancer 2000;88(12 Suppl.):2961–78.

[79] Fleisch H. Development of bisphosphonates. Breast Cancer Res 2002;4:30–4.

[80] Brown JE, Ellis SP, Lester JE, Gutcher S, Khanna T, Purohit OP, et al. Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid. Clin Cancer Res 2007;13:5406–10.

[81] Hughes DE, Wright KR, Uy HL, Sasaki A, Yoneda T, Roodman GD, et al. Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. J Bone Miner Res 1995;10(10):1478–87.

[82] Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 2008;19(6):733–59.

[83] Daubiné F, Le Gall C, Gasser J, Green J, Clézardin P. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. J Natl Cancer Inst 2007;99(4):322–30.

[84] Pavlakis N, Schmidt RL. Stockler MR bisphosphonates for breast cancer. Cochrane Database Syst Rev 2005;3:CD003474.
[85] Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. J Clin Oncol 1996;14(9):2552–9.
[86] Hultborn R, Gundersen S, Ryden S, Holmberg E, Carstensen J, Wallgren UB, et al. Efficacy of pamidronate in breast cancer with bone metastases: a randomized, double–blind placebo–controlled multicenter study. Anticancer Res 1999;19(4C):3383–92.
[87] Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, Mellars K, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer 2000;88(5):1082–90.
[88] Body JJ, Diel IJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 2003;14:1399–405.
[89] Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001;7(5):377–87.
[90] Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003;98(8):1735–44.
[91] Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, Iino Y, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. J Clin Oncol 2005;23(15):3314–21.
[92] Body JJ, Bartl R, Burckhardt P, Delmas PD, Diel IJ, Fleisch H, et al. Current use of bisphosphonates in oncology. International Bone and Cancer Study Group. J Clin Oncol 1998;16(12):3890–9.
[93] Ralston SH, Coleman R, Fraser WD, Gallagher SJ, Hosking DJ, Iqbal JS, et al. Medical management of hypercalcemia. Calcif Tissue Int 2004;74(1):1–11.
[94] Rosner MH, Dalkin AC. Onco-nephrology: the pathophysiology and treatment of malignancy-associated hypercalcemia. Clin J Am Soc Nephrol 2012;7(10):1722–9.
[95] Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19(2):558–67.
[96] Body JJ, Diel IJ, Lichinitzer M, Lazarev A, Pecherstorfer M, Bell R, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer 2004;90:1133–7.
[97] Diel IJ, Body JJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, , et alMF 4265 Study Group. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 2004;40(11):1704–12.
[98] Wardley A, Davidson N, Barrett-Lee P, Hong A, Mansi J, Dodwell D, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. Br J Cancer 2005;92:1869–76.
[99] Cartenì G, Bordonaro R, Giotta F, Lorusso V, Scalone S, Vinaccia V, et al. Efficacy and safety of zoledronic acid in patients with breast cancer metastatic to bone: a multicenter clinical trial. Oncologist 2006;11(7):841–8.
[100] Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev 2012;2:CD003474.
[101] Sheridan JP, Marsters SA, Pitti RM, Gurney A, Skubatch M, Baldwin D, et al. Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. Science 1997;277(5327):818–21.
[102] Body JJ, Facon T, Coleman RE, Lipton A, Geurs F, Fan M, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res 2006;12(4):1221–8.
[103] Gnant M, Clézardin P. Direct and indirect anticancer activity of bisphosphonates: a brief review of published literature. Cancer Treat Rev 2012;38(5):407–15.
[104] Ben-Aharon I, Vidal L, Rizel S, Yerushalmi R, Shpilberg O, Sulkes A, et al. Bisphosphonates in the adjuvant setting of breast cancer therapy-effect on survival: a systematic review and meta-analysis. PLoS One 2013;8(8):e70044.
[105] Azim H, Azim Jr HA. Targeting RANKL in breast cancer: bone metastasis and beyond. Expert Rev Anticancer Ther 2013;13(2):195–201.
[106] Azim HA, Kamal NS, Malak RA. Bisphosphonates in the adjuvant treatment of young women with breast cancer: the estrogen rich is a poor candidate! J Thorac Dis 2013;5(Suppl. 1):S27–35.
[107] Fizazi K, Lipton A, Mariette X, Body JJ, Rahim Y, Gralow JR, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol 2009;27:1564–71.
[108] Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, 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):813–22.
[109] Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, 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):5132–9.
[110] Vadhan-Raj S, von Moos R, Fallowfield LJ, Patrick DL, Goldwasser F, Cleeland CS, et al. Clinical benefit in patients with metastatic bone disease: results of a phase 3 study of denosumab versus zoledronic acid. Ann Oncol 2012;23(12):3045–51.
[111] 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.
[112] Cleeland CS, Body JJ, Stopeck A, von Moos R, Fallowfield L, Mathias SD, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer 2013;119(4):832–8.
[113] Stopeck AT, Lipton A, Martín M, Body J-J, Paterson A, Steger GG, et al. Denosumab in patients with breast Cancer and bone metastases previously treated with zoledronic acid or denosumab: results from the 2-Year open-label extension treatment phase of a pivotal phase 3 study. San Antonio, TX: Poster presentation at 34th Annual San Antonio Breast Cancer Symposium; December, 2011.
[114] Olson K, Van Poznak C. Significance and impact of bisphosphonate-induced acute phase responses. J Oncol Pharm Pract 2007;13(4):223–9.
[115] Miyagawa F, Tanaka Y, Yamashita S, Minato N. Essential requirement of antigen presentation by monocyte lineage cells for the activation of primary human gamma delta T cells by aminobisphosphonate antigen. J Immunol 2001;166(9):5508–14.
[116] Green AE, Lissina A, Hutchinson SL, Hewitt RE, Temple B, James D, et al. Recognition of nonpeptide antigens by human V gamma 9V delta 2 T cells requires contact with cells of human origin. Clin Exp Immunol 2004;136(3):472–82.
[117] Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins. Clin Exp Immunol 2005;139(1):101–11.
[118] Peddi P, Lopez-Olivo MA, Pratt GF, Suarez-Almazor ME. Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. Cancer Treat Rev 2013;39(1):97–104.
[119] Body JJ. The risk of cumulative renal effects of intravenous bisphosphonates. Support Cancer Ther 2006;3(2):77–83.
[120] Coleman RE, McCloskey EV. Bisphosphonates in oncology. Bone 2011;49(1):71–6.
[121] Novartis. Zometa® (zoledronic acid) injection [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2011.
[122] Roche. Bonviva® (ibandronate) [prescribing information]. Nutley, New Jersey: Roche Therapeutics Inc.; 2010.
[123] Fallowfield L, van Moos R, Costa L, Stopeck A, Clemons M, Clarke N, et al. Weighing bone-targeted treatment options for patients with solid tumours and skeletal complications from metastatic disease. Eur Oncol Haematol 2012;8(3):148–55.
[124] Mortimer JE, Pal SK. Safety considerations for use of bone-targeted agents in patients with cancer. Semin Oncol 2010;37(Suppl. 1):S66–72.
[125] Block GA, Bone HG, Fang L, Lee E, Padhi D. A single–dose study of denosumab in patients with various degrees of renal impairment. J Bone Miner Res 2012;27(7):1471–9.
[126] Amgen. Xgeva® (denosumab) prescribing information. Thousand Oaks, CA: Amgen Inc.; 2010.
[127] Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. Ann Oncol 2006;17(6):897–907.
[128] Stopeck AT, Lipton A, Martin M, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Cancer Res 2011;71(24 Suppl.). Abstract nr P3-16-07.
[129] Coleman RE. Risks and benefits of bisphosphonates. Br J Cancer 2008;98(11):1736–40.
[130] Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 2008;23(6):826–36.
[131] Fusco V, Galassi C, Berruti A, Ortega C, Ciuffreda L, Scoletta M, et al. Decreasing frequency of osteonecrosis of the jaw in cancer and myeloma patients treated with bisphosphonates: the experience of the Oncology Network of Piedmont and Aosta Valley (North-Western Italy). ISRN Oncol 2013;2013:672027.
[132] Woo S-B, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006;144(10):753–61.
[133] Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, et al. Practical guidelines for the prevention, diagnosis, and treatment of

osteonecrosis of the jaw in patients with cancer. J Oncol Pharm Pract 2006;2(1):7–14.
[134] Ripamonti CI, Maniezzo M, Campa T, Fagnoni E, Brunelli C, Saibene G, et al. Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. Ann Oncol 2009;20(1):137–45.
[135] Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol 2011;29(9):1221–7.
[136] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer. v.2.2013. Fort Washington, PA: National Comprehensive Cancer Network, Inc; 2013 [accessed 03.02.13]. Available from: http://www.nccn.org.
[137] Cardoso F, Fallowfield L, Costa A, Castiglione M, Senkus E, ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011;22(Suppl. 6):vi25–30.
[138] Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). Breast 2012;21(3):242–52.
[139] Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423–36.
[140] Hellman S, Weichselbaum RR. Oligometasetases. J Clin Oncol 1995;13(1):8–10.
[141] Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol 2011;8(6):378–82.
[142] Niibe Y, Kuranami M, Matsunaga K, Takaya M, Kakita S, Hara T, et al. Value of high-dose radiation therapy for isolated osseous metastasis in breast cancer in terms of oligo-recurrence. Anticancer Res 2008;28(6B):3929–31.
[143] Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, et al. Stereotactic body radiotherapy for oligometastases. Lancet Oncol 2013;14(1):e28–37.
[144] Lipton A. Biochemical bone markers in breast cancer. Cancer Treat Rev 2006;32((Suppl. 1):20–2.
[145] de la Piedra C, Alcaraz A, Bellmunt J, Meseguer C, Gómez-Caamano A, Ribal MJ, et al. Usefulness of bone turnover markers as predictors of mortality risk, disease progression and skeletal-related events appearance in patients with prostate cancer with bone metastases following treatment with zoledronic acid: TUGAMO study. Br J Cancer 2013;108(12):2565–72.
[146] Love C, Din AS, Tomas MB, Kalapparambath TP, Palestro CJ. Radionuclide bone imaging: an illustrative review. Radiographics 2003;23(2):341–58.
[147] Padhani AR, Gogbashian A. Bony metastases: assessing response to therapy with whole–body diffusion MRI. Cancer Imaging 2011;11(Spec No A):S129–45.
[148] Kircher MF, Hricak H, Larson SM. Molecular imaging for personalized cancer care. Mol Oncol 2012;6(2):182–95.
[149] Ruggiero SL, Mehrotra B. Bisphosphonate-related osteonecrosis of the jaw: diagnosis, prevention, and management. Annu Rev Med 2009;60:85–96.
[150] Clemons MJ, Dranitsaris G, Ooi WS, Yogendran G, Sukovic T, Wong BY, et al. Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. J Clin Oncol 2006;24:4895–900.
[151] Clemons M, Dranitsaris G, Ooi W, Cole DE. A phase II trial evaluating the palliative benefit of second-line oral ibandronate in breast cancer patients with either a skeletal related event (SRE) or progressive bone metastases (BM) despite standard bisphosphonate (BP) therapy. Breast Cancer Res Treat 2009;108:79–85.
[152] Amir E, Whyne C, Freedman OC, Fralick M, Kumar R, Hardisty M, et al. Radiological changes following second–line zoledronic acid treatment in breast cancer patients with bone metastases. Clin Exp Metastasis 2009;26(5):479–84.
[153] Amadori D, Aglietta M, Alessi B, Gianni L, Ibrahim T, Farina G, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol 2013;14(7):663–70.
[154] Coleman RE, Wright J, Purohit O, Huston S, Agrawal R, Hayward L, et al. Randomized trial of marker directed versus standard schedule of zoledronic acid for bone metastases from breast cancer. Proc Am Soc Clin Oncol 2012;30(Suppl.). abstr 511.
[155] Lipton A, Steger GG, Figueroa J, Alvarado C, Solal-Celigny P, Body JJ, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. J Clin Oncol 2007;25(28):4431–7.
[156] Yonemori K, Fujiwara Y, Minami H, Kitagawa K, Fujii H, Arai T, et al. Phase 1 trial of denosumab safety, pharmacokinetics, and pharmacodynamics in Japanese women with breast cancer-related bone metastases. Cancer Sci 2008;99(6):1237–42.
[157] Montefusco V, Gay F, Spina F, Miceli R, Maniezzo M, Teresa Ambrosini M, et al. Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. Leukemia Lymphoma 2008;49(11):2156–62.
[158] Hellstein JW, Adler RA, Edwards B, Jacobsen PL, Kalmar JR, Koka S, et al. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc 2011;142(11):1243–51.
[159] European Medicines Agency. CHMP assessment report on bisphosphonates and osteonecrosis of the jaw. Procedure under Article 5(3) of Regulation (EC) No 726/2004. London; 2009.
[160] Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate–related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007;65(3):369–76.
[161] Patel V, McLeod NM, Rogers SN, Brennan PA. Bisphosphonate osteonecrosis of the jaw—a literature review of UK policies versus international policies on bisphosphonates, risk factors and prevention. Br J Oral Maxillofac Surg 2011;49(4):251–7.
[162] Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012;23(5):1341–7.