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SPECIAL ARTICLE

Bone health in cancer: ESMO Clinical Practice Guidelines†

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INTRODUCTION

Cancer and its treatment can have profound effects on bone health. Clinicians treating cancer patients need to be aware of the multidisciplinary treatments available to reduce skeletal morbidity from metastatic disease and minimise cancer treatment-induced damage to the normal skeleton. These guidelines provide a framework for maintaining bone health in patients with cancer.

INCIDENCE, EPIDEMIOLOGY AND CLINICAL CONSEQUENCES

Metastatic bone disease is most commonly seen with specific cancer types—notably those with metastasis from the breast (70%), prostate (85%), lung (40%) and kidney (40%)—as well as multiple myeloma (MM) (95%).[1] Bone metastases most frequently affect the axial skeleton and often cause skeletal complications known as skeletal-related events (SREs): pathological fracture, radiotherapy (RT) to bone, surgery to bone, spinal cord compression (SCC) and hypercalcaemia, although the last may be of paraneoplastic origin and occur without bone metastases. RT and fractures are the most common SREs, reflecting the burden of bone pain and structural damage caused by metastatic involvement. Typically, SREs are associated with loss of mobility and social functioning, reduced quality of life (QoL), increased health care expenditure and worse survival.[2]

Across all tumour types, patients with breast cancer have the highest incidence of SREs.[1] In prostate cancer, despite the osteosclerotic nature of bone metastases, SREs are still very common. Histomorphometric studies in prostate cancer have demonstrated increased osteolysis within the affected bone and bone resorption biomarkers are often increased.[3] Bone pain—most often in the back due to vertebral fractures—is a presenting feature in three-quarters of MM patients. Extensive lytic lesions are frequent and typically do not heal despite successful anti-neoplastic treatment. Diffuse osteoporosis can also be a presenting feature in MM.[4]

PATHOPHYSIOLOGY

The process of cancer metastasis is extraordinarily complex and only partially understood. Preparation of the pre-metastatic niche by tumour-derived exosomes, microRNAs and growth factors precedes the release of cells from the primary tumour.[5] Most disseminated tumour cells (DTCs) die, but a few survive, and the bone marrow microenvironment may act as a favourable environment for colonisation by malignant cells. Haematopoietic stem cell, osteoblastic and vascular niches within the bone microenvironment have all been suggested as sanctuary sites for DTCs.[5] Thereafter, DTCs can enter a dormant non-proliferating state sometimes, particularly in breast and prostate cancers, for many years. How and why cells emerge from dormancy and initiate the development of overt metastases is not well understood.

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Proliferating tumour cells in the bone microenvironment have the capacity to produce a range of cytokines and growth factors that increase osteoblast production of receptor activator of nuclear factor kappa B ligand (RANKL). This leads to activation of osteoclasts and disturbance of normal coupling of bone formation and bone resorption. Bone-derived growth factors are released during bone resorption and may stimulate proliferation of the tumour cell population, and thus create a self-sustaining vicious cycle between cancer cells and the bone microenvironment.[5]

DIAGNOSIS AND MONITORING

Metastatic involvement of the skeleton typically affects multiple sites and causes pain and bony tenderness. The diagnosis is often straightforward but confusion with benign pathology is particularly problematic in elderly patients due to degenerative disease and osteoporosis.

Imaging technologies for diagnosis and monitoring of bone metastasis have increased during recent years.[6] Imaging can be divided into predominantly structural modalities such as plain radiographs, computed tomography (CT), magnetic resonance imaging (MRI) or metabolic and molecular imaging tools including diffusion-weighted MRI (DW-MRI), positron emission tomography (PET) and single-photon emission CT (SPECT).

Structural imaging

Plain radiographs are an insensitive test for metastasis. For a destructive lesion in trabecular bone to be recognised, it must be >1 cm in diameter with loss of $\sim 50\%$ of the bone mineral content.

CT produces images with excellent tissue and contrast resolution. Bony destruction and sclerosis as well as any soft tissue extension are usually easily visualised. CT is particularly useful to localise lesions for biopsy. However, differentiation between metabolically active versus inactive bone lesions cannot be made, limiting its use for evaluation of treatment effects.

Detection of bone metastases by MRI depends on differences in signal intensity between tumour tissue and bone marrow. Metastatic tumour is visualised directly, in contrast with the indirect changes observed by X-ray or radionuclide bone scanning. Like CT, MRI is useful for evaluating patients with positive bone scans and normal radiographs and for elucidating the cause of a vertebral compression fracture. MRI is more sensitive than bone scintigraphy for detection of spinal metastases and essential for treatment decision-making in patients with SCC.

Metabolic and molecular imaging

Nuclear medicine technologies use radiolabelled tracers for imaging of metabolic or molecular characteristics of bone metastatic disease. These can be classified as osteotropic (bone-seeking) agents that image the osteoblastic reaction induced by metastasis or oncotropic (direct tumour imaging) agents that assess the metabolic or molecular characteristics. The radionuclide bone scan uses a technetium-99 (^{99}Tc)-labelled bone-seeking bisphosphonate with preferential uptake of tracer at sites of active bone formation that reflects the metabolic reaction of bone to any underlying disease process. When bone metastases develop there is usually sufficient reactive new bone formation to produce a focal increase in tracer uptake, often before bone destruction can be seen on radiographs. With the exception of patients with MM, the bone scan is more sensitive than plain radiographs for the detection of skeletal pathology.

PET imaging has significant advantages over bone scintigraphy for evaluation of skeletal metastatic disease, including superior diagnostic accuracy, higher spatial resolution and shorter imaging times. However, PET is not 100% specific for skeletal metastasis and requires careful integration of morphological changes in bone on CT or MRI to ensure accurate interpretation.

^{18}F-fluorodeoxyglucose (FDG)-PET-CT is the most widely available technique and is based on the increased aerobic glycolysis of most intermediate and high-grade cancer lesions. Typically, untreated lytic lesions demonstrate greater FDG uptake than osteosclerotic metastases, although slowly proliferating lesions can be missed. FDG-PET allows accurate differentiation between progressive osteosclerosis on CT that can reflect either tumour progression or response to therapy.

^{18}F-sodium fluoride is the most accurate osteotropic PET imaging agent; it is superior to ^{99}Tc bone scintigraphy and SPECT and comparable to DW-MRI for diagnosis.[6] However, the agent is expensive and not widely available. Other tracers are combined with tumour-specific targets, such as a prostate-specific membrane antigen (PSMA) in prostate cancer [e.g. gallium-68(^{68}Ga)-anti-PSMA] or somatostatin receptors in neuroendocrine neoplasms (e.g. ^{68}Ga-DOTATATE).

The diagnostic pathway for MM is somewhat different, as myeloma bone disease is often missed on radionuclide bone scans. In addition to bone marrow biopsy, low-dose whole-body CT or FDG-PET-CT imaging are preferred imaging modalities in MM.[7]

Bone biopsy

A diagnosis of metastatic bone disease has major clinical and emotional consequences for the patient concerned and it is vital that the diagnosis is always accurate. When accompanied by definite metastatic disease at other sites, the need for confirmation of bone involvement is less important. However, in bone-only disease, especially when there are few lesions or imaging tests are equivocal, histological confirmation of metastatic disease is strongly recommended. CT-guided biopsy of the suspicious area(s) when feasible should be carried out, followed by pathological assessment by a specialist familiar with the technical challenges of working with bone. Biopsy also provides the opportunity to reassess biomarkers that may direct future therapies.

Evaluation

Bone is the only site of metastatic disease that has separate criteria for evaluation of response to treatment, based on bone repair and destruction rather than on changes in tumour volume. Assessing response in bone metastases is difficult and the healing processes are slow to evolve and are quite subtle, only beginning to appear after 3–6 months and taking more than a year to mature.

A complete review of imaging since the start of a treatment is necessary to reliably evaluate treatment response. Sclerosis of lytic metastases with no radiological evidence of new lesions constitutes tumour regression (a partial response). Confounding factors include the appearance of sclerosis in an area that was previously normal. This could represent progression but may also reflect healing within a lesion that was present at the start of treatment but not large enough to be visible radiographically. Bone metastases measuring $\leq$10 mm (the large majority) without soft tissue masses are designated as unmeasurable, thereby excluding most patients with bone-only metastatic disease from the majority of new drug trials.

The use of bone scanning for assessment of response to therapy is unreliable when lytic metastases predominate. During successful therapy, the healing processes cause an initial increase in tracer uptake (the flare response) and scans carried out during this phase are likely to show both increased intensity of existing lesions and new 'hot spots'. After treatment for 6 months, the bone scan appearances may improve, as the increased production of immature new bone ceases. In prostate cancer, where response assessment is particularly challenging, a methodology for allowing for this flare response has been devised, which allows bone scans to be used for response evaluation in sclerotic metastases.[8]

FDG-PET-CT imaging is the most accurate way of assessing treatment response of hypermetabolic bone metastasis and is based on the quantitative assessment of FDG uptake immediately before, during and after therapy. Metabolic treatment-induced effects appear much earlier than morphological changes and facilitate rapid treatment adaptation.

The PET Response Criteria in Solid Tumours (PERCIST) criteria are now widely accepted, with partial response requiring a drop of 30% of the most active bone (or other) lesion.[9] Correlation of metabolic response with disease outcomes has been documented in tumours that have high FDG uptake at baseline. However, use of FDG-PET-CT in prostate cancer is not generally recommended, as increased FDG uptake is only observed in late and aggressive disease stages.

Bone biomarkers

Both bone resorption and formation result in release of biochemical markers that are measurable in blood or urine.[10] These include the cross-linked collagen peptides that are breakdown products from osteolysis and the terminal peptides that are cleaved from procollagen before integration into new bone matrix.

Biochemical markers of bone metabolism reflect ongoing rates of bone resorption and formation in the body as a whole and do not provide information specific to individual lesions. Elevated levels of a bone biomarker may support a diagnosis of bone metastases, but sensitivity and specificity are low and they do not have a clear role in routine patient follow-up.

Recommendations

- The diagnostic algorithm shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.07.019, should be applied for the investigation of clinical symptoms of possible bone metastasis [V, A].
- Review of all imaging, alongside clinical information and, when available, biopsy findings should be evaluated by a multidisciplinary team [V, A].
- CT and MRI are the modalities of choice for routine response assessment of bone metastases and bone lesions from MM [II, A].
- For early evaluation of response, FDG-PET/CT imaging is valuable in most disease settings [II, B].
- Bone biomarkers can provide prognostic information but are not recommended for routine patient follow-up [III, D].

TREATMENT

Principles of multidisciplinary management

Treatment of bone metastases is aimed at preventing disease progression and symptom palliation; cure is only a realistic aim in rare tumours affecting bone (e.g. lymphoma). Treatments vary depending on the underlying disease. External beam RT (EBRT), endocrine treatments, chemotherapy (ChT) and targeted and immunological therapies as well as systemically administered radioisotopes are all potentially important. Treatment decisions depend on whether the bone disease is localised or widespread, on the presence or absence of extraskeletal metastases and the nature of the underlying malignancy. Resistance to systemic treatments can be expected to develop, necessitating periodic changes of therapy in an effort to regain control of the disease. In addition, surgical intervention may be necessary for the structural complications of bone destruction or nerve compression. Bone-targeted agents (BTAs) are included to reduce morbidity and complement these treatment modalities.

Optimal management requires a multidisciplinary team that includes medical and radiation oncologists, (orthopaedic) surgeons, (interventional) radiologists, nuclear medicine physicians and palliative medicine specialists with expertise in bone complications from cancer.

Palliative RT

Local EBRT is effective for relieving painful bone metastases. Overall response rates (ORRs) of 70%–80% are reported,

with complete relief of pain in one-third of patients. Pain relief may occur rapidly, with 40% of responders showing benefit within 10 days.[11] Meta-analyses have shown no difference in pain control between fractionated treatment and a single fraction in uncomplicated bone metastases.[11] Guidelines recommend single-fraction RT in patients with painful uncomplicated bone metastases due to convenience for patients and caregivers. However, the need for retreatment may be higher after single-fraction regimens. Re-irradiation is effective, and a single fraction for retreatment improves QoL and is less toxic than longer regimens.[11]

Side-effects of palliative RT for bone metastases depend on the body area treated. Antiemetic prophylaxis is recommended when radiation is over emetogenic areas. An initial flare in bone pain is common and can be reduced by prophylactic treatment with dexamethasone alongside analgesics.

SCC is a medical emergency requiring urgent MRI to confirm the diagnosis. Patients should start 16—24 mg dexamethasone per day without delay and, if possible, steadily reduce over 2 weeks. In patients with good performance status (PS), limited disease and a single area of compression, a surgical opinion should be requested to determine suitability for a surgical intervention, followed by RT. In patients who are not suitable for surgery, RT alone is indicated, with a single 8-Gy fraction sufficient for those with a poor prognosis. A prolonged fractionation schedule is restricted to those being considered for local control.[12]

In patients with good PS, pathological or impending pathological fractures of the extremities are preferentially treated with orthopaedic surgery to fix or prevent fracture. Postoperative fractionated RT is usually recommended to prevent prosthesis failure and reduce the need for subsequent surgery. In patients who have extremely short life expectancies, RT alone may be considered for pain relief, although it does not restore bone stability. Patients receiving surgery for spinal metastases can also be offered RT postoperatively, with evidence that EBRT or stereotactic body RT (SBRT) can improve local control and ambulation in these patients.

Radionuclide therapy

Targeted RT using systemic radioisotopes permits more specific delivery of the radiation dose to multiple tumour sites with relative sparing of normal tissues compared with EBRT. A prime example is thyroid follicular carcinoma with bone metastases. Here, treatment of bone metastases with iodine-131 (^{131}I) is well established.

In prostate and breast cancers with osteoblastic skeletal metastases, palliation of bone pain has been demonstrated with bone-seeking beta emitters such as strontium chloride-89 ($^{89}SrCl_2$) and samarium-153 lexidronam-labelled ethylenediaminetetramethylene phosphonic acid (^{153}Sm-EDTMP). However, bone marrow toxicity makes repeated treatments problematic and the lack of survival benefit limits clinical use.

More recently, the bone-seeking alpha particle-emitting radiopharmaceutical radium-223 (^{223}Ra) was approved for use in bone-predominant, metastatic castration-resistant prostate cancer (mCRPC).[13] The alpha particles provide a high-energy radiation dose to cells close to bone surfaces and the mesh of osteoblastic stroma within the metastasis. In the ALSYMPCA trial, patients with symptomatic, bone-dominant disease who failed or were deemed unfit for docetaxel received ^{223}Ra or placebo every 4 weeks in addition to best standard care. ^{223}Ra significantly improved overall survival (OS) by 3.6 months and delayed new symptomatic skeletal events (SSEs) by 5.8 months.[13] Benefits were larger among patients treated with prior and/or concomitant use of bisphosphonates. Clinical benefit from ^{223}Ra occurred regardless of prior docetaxel use and produced significant improvement in patient QoL and fewer hospitalisations than placebo. Myelosuppression and diarrhoea were the most frequent adverse events (AEs) associated with ^{223}Ra.[13]

Due to non-overlapping mechanisms of actions, ^{223}Ra is under clinical evaluation in combinations with hormonal agents targeting the androgen receptor axis. In the ERA-223 trial,[14] the addition of ^{223}Ra to abiraterone acetate plus steroids did not improve SSE-free survival (the primary end point) in patients with castration-resistant prostate cancer (CRPC). Furthermore, the trial was terminated early and unblinded due to an increased frequency of osteoporotic fractures compared with placebo. This was most striking in patients not receiving a BTA at enrolment. The use of this combination is not recommended and, based on these results and experience with combined enzalutamide and ^{223}Ra, a BTA should be started before ^{223}Ra.

A new and evolving radionuclide therapy approach is based on theranostic selection of patients using an indium-111 (^{111}In)-labelled antibody to cell surface markers such as PSMA. Tumours shown to be PSMA-positive can benefit from the use of PSMA-targeted ligands linked to therapeutic radiopharmaceuticals, e.g. lutetium-177 (^{177}Lu) or actinium-225 (^{225}Ac).[15]

Orthopaedic surgery

The predominant goals of surgical treatment are to maintain patient functionality and mobility by relieving pain preventing impending fractures and/or neural compression or stabilising a pathological fracture. Pathological fracture and severe pain are clear indications for surgery. For an impending fracture, the management is more controversial. Aspects to consider include the underlying primary tumour and its biological behaviour in bone, the likely efficacy of available treatment(s) and patient comorbidities. There are many different surgical tools for osteosynthesis and reconstruction of bony defects and the selected procedure should aim to be safe, short and simple.

Solitary or oligometastasis and small lesions should ideally be excised completely to avoid further local recurrence and complications. However, in most cases an intralesional approach is unavoidable.

In the proximal femur and humerus, a long-stem cemented or modular tumour endoprosthesis is preferred

to facilitate rapid mobilisation. With acetabular involvement, the surgical approach is adapted to the severity and location of destruction using implants from revision hip surgery. In the diaphysis of a long bone, a plate, an intramedullary nail or a prosthesis may be implanted.

For short-term life expectancies, intramedullary nailing with locking screws introduced by a minimally-invasive technique—and if necessary augmented by bone cement—is recommended. This construct allows immediate full weight-bearing of the extremity. Tumour spread along the nail track needs to be considered, and nailing avoided in patients with a good prognosis and/or a radioresistant tumour.[16]

Prophylactic stabilisation of impending fractures is generally preferred to fixation after fracture as functional recovery is better, inpatient stays are shorter and surgical complications fewer. Prophylactic surgery is generally recommended for lesions $\geq$30 mm in greatest dimension, lytic destruction of $\geq$50% of the cortex of a long bone and continued pain with weight-bearing after RT. Mirels' scoring system based on anatomic site, pain pattern, radiographic nature and lesion size can be helpful in estimating the risk of pathological fractures.[16] Biomechanical assessment of fracture risk using CT imaging shows promise but is not yet in routine use.

Bone-targeted agents

Currently available BTAs—bisphosphonates and denosumab—are potent inhibitors of bone resorption. Bisphosphonates are analogues of pyrophosphate that concentrate in active bone remodelling sites. During bone resorption, active osteoclasts ingest the bisphosphonate by endocytosis and undergo cell death. Non-nitrogen-containing bisphosphonates (e.g. clodronate) act through cytotoxic effects on osteoclasts whereas nitrogen-containing bisphosphonates (e.g. pamidronate, ibandronate and zoledronate) have a direct apoptotic effect.[3] In addition, bisphosphonates may also have antitumour and/or antiangiogenic effects, although the clinical relevance of these preclinical observations is controversial.[3]

Denosumab is a monoclonal antibody that binds avidly to RANKL, preventing its interaction with its receptor RANK[17] and causing rapid suppression of bone resorption. RANKL inhibition may also exert antitumour effects and decreases mammary carcinogenesis in preclinical models.[17] Again, the clinical relevance of these preclinical observations is unclear.

Although RT is the treatment of choice for localised bone pain, BTAs provide an additional treatment approach for the relief of bone pain that is of similar magnitude to RT and useful across different tumour types.[3]

In patients with bone metastases, BTAs are used to reduce the risk of SREs as well as to treat hypercalcaemia of malignancy. Multiple randomised clinical trials (RCTs) have clearly demonstrated that they are effective in reducing skeletal morbidity from metastatic cancer[2,3] (see Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.07.019).

In selecting a BTA, the drug, dose and dosing interval need to be assessed on an individual patient basis including the risk for an SRE and the overall status of control of the tumour. Factors that may be influential include access to agents, route of administration and patient preference. From efficacy, convenience and renal health perspectives, denosumab is the preferred agent. However, from a health economic standpoint, generic bisphosphonates are more cost effective and the issue of rebound osteolysis on denosumab discontinuation described below does not occur with bisphosphonates (Figure 1). Since the trials leading to the approval of BTAs were carried out, many new targeted therapies have emerged. However, the risk for SREs persists and inclusion of BTAs remain an important component of current management.

There are no randomised data to guide whether all patients with bone metastases should initiate a BTA as soon as bone metastases are diagnosed. Additionally, there is no approved tool to predict which patients will develop an SRE. However, a first SRE often occurs early in the course of metastatic bone disease. In a pivotal trial comparing denosumab with zoledronate, 37% of patients had already experienced an SRE at study inclusion at a median time of only 2 months from initial diagnosis of bone metastases.[18] Following careful explanation of the benefits and risks to the patient, the authors recommend starting a BTA in the vast majority of patients as soon as bone metastases are diagnosed and whether they are symptomatic or not.

BTAs should normally continue indefinitely, including into the hospice setting, although in many cases their use—with associated monitoring—may decline as end-of-life care takes over. However, treatment may be interrupted in patients with good prognostic features such as oligometastatic disease, a perceived low risk of bone complications and durable response to systemic treatment. The optimal dosing frequency is discussed later.

Breast cancer. RCTs with pamidronate infusions for $\leq$2 years in addition to ChT or hormonal therapy in breast cancer patients with at least one lytic bone metastasis demonstrated that bisphosphonates can reduce skeletal morbidity rate by more than one-third, increase the median time to the occurrence of the first SRE by almost 50% and reduce the proportion of patients having any SRE.[3] Subsequently, more convenient and effective amino-bisphosphonates have emerged including zoledronate and both intravenous (i.v.) and oral ibandronate.[3] Zoledronate achieved the pre-established criterion for non-inferiority to pamidronate and in a subsequent multiple-event analysis, was shown to reduce the SRE risk by an additional 20% compared with that achieved by pamidronate.[19] Oral ibandronate failed to achieve non-inferiority to zoledronate in reducing the overall risk for SRE but was similar in delaying time to the first event and provides a useful oral alternative to parenteral treatments.[20]

Denosumab was evaluated in three identical, double-blind, phase III trials in bisphosphonate-naive patients with bone metastases. Patients received four weekly

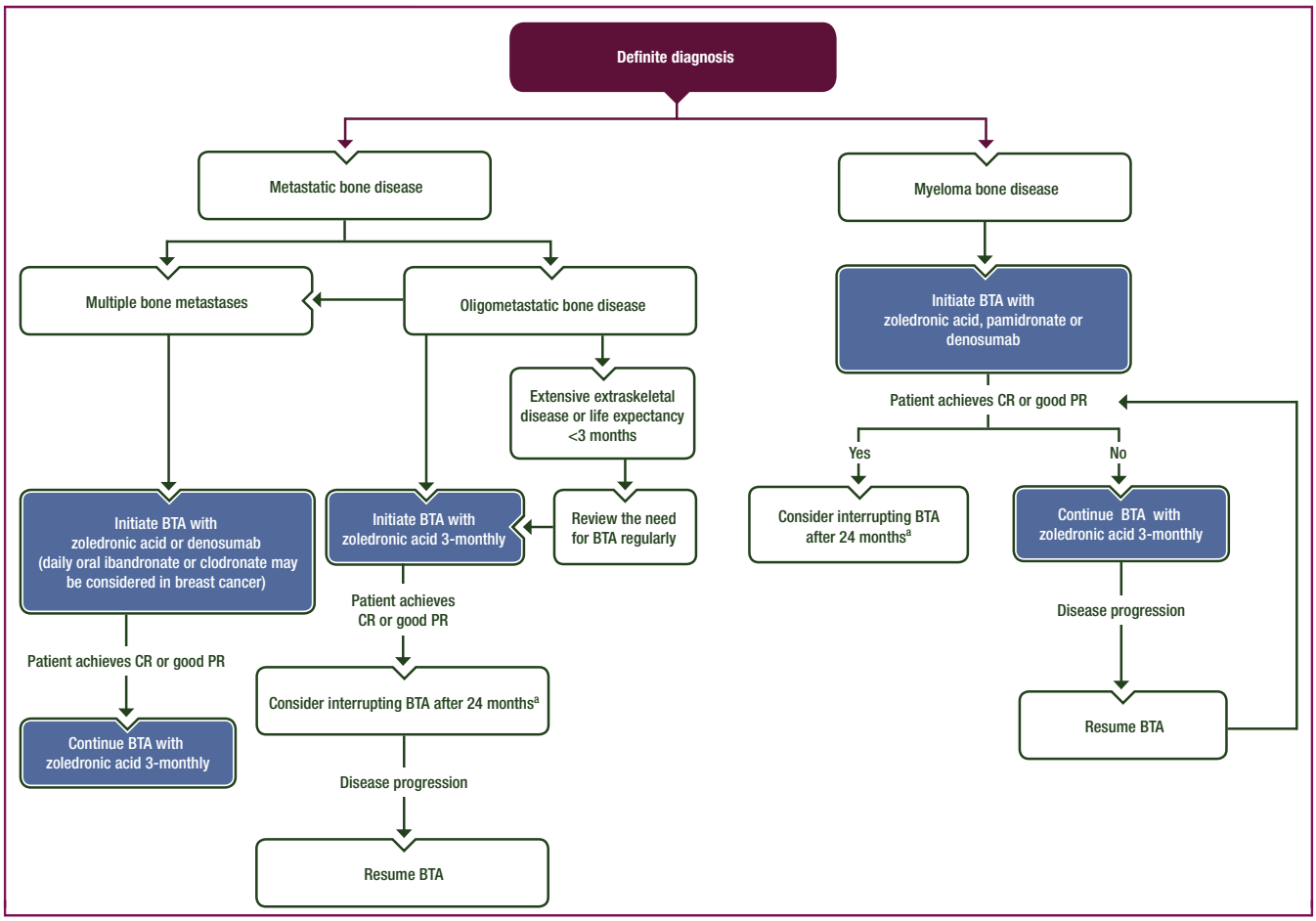

Figure 1. Algorithm for use of bone-targeted treatments for bone metastases and myeloma bone disease.
BTA, bone-targeted agent; CR, complete response; PR, partial response.
[a] See the recommendations about discontinuation of denosumab in the text.

injections of denosumab [120 mg subcutaneous (s.c.)] or zoledronate (4 mg i.v.), with supplements of calcium and vitamin D.[2] The primary end point was the time to first SRE. In patients with bone metastases secondary to breast cancer, denosumab was statistically superior to zoledronate in delaying both the first and subsequent SREs and delayed worsening of bone pain.[2]

Prostate cancer. Zoledronate is the only bisphosphonate to demonstrate a significant reduction in SRE in patients with CRPC.[3] Zoledronate reduced the overall risk of skeletal complications by 36% and reduced bone pain at all time points. In the randomised trial comparing denosumab to zoledronate in men with bone metastases from CRPC, denosumab delayed the time to first SRE and produced an 18% reduction in cumulative SREs over zoledronate.[2]

In endocrine-sensitive prostate cancer (ESPC), the addition of zoledronate to first-line long-term hormone therapy (STAMPEDE trial) showed no evidence of survival improvement.[3] Furthermore, in the CALGB 90202 study comparing zoledronate to placebo in ESPC with SREs as the primary end point, early treatment with zoledronate did not significantly reduce their frequency.[3]

Other solid tumours. There are relatively few randomised data on the use of BTAs in lung cancer and other solid tumours with bone metastases. However, in a placebo-controlled trial of zoledronate in patients with skeletal metastases from cancers other than the breast or prostate, treatment with zoledronate significantly reduced the number of SREs and prolonged the time to first event.[3] *Post hoc* analyses suggested that treatment with zoledronate was associated with improved survival in patients with lung cancer, especially in those with high levels of bone resorption markers.[21] It is likely, in these poor prognosis patients, that prevention of skeletal morbidity avoided delays in the initiation and continued delivery of life-prolonging anticancer treatments.

Denosumab has also been studied in this population of patients with metastatic bone disease and confirmed non-inferiority of denosumab to zoledronate.[2] An exploratory analysis of the patients with non-small-cell lung cancer suggested improvement in survival with denosumab, although this observation was not supported by the recently reported SPLENDOUR trial, see additional supplementary References, available at https://doi.org/10.1016/j.annonc.2020.07.019.

Multiple myeloma. BTAs are an integral part of the treatment of MM. The Cochrane Myeloma Review Group concluded that both pamidronate and clodronate reduce the incidence of hypercalcaemia, the pain index and the number of vertebral fractures in MM patients.[22] The typical

dose of pamidronate is 90 mg every 3—4 weeks, but lower doses may be adequate.

Zoledronate has comparable efficacy to pamidronate[19] but is clearly superior to daily oral clodronate. In the Myeloma IX trial of patients with newly diagnosed MM, fewer patients receiving zoledronate developed SREs before progression. Zoledronate also reduced the risk of SREs relative to clodronate. Most importantly, in comparison to clodronate, the addition of zoledronate to standard first-line antimyeloma therapy prolonged median survival by 6 months.[23]

Denosumab has been compared with zoledronate in newly diagnosed MM patients. Denosumab was statistically noninferior to zoledronate in delaying time to first SRE and extended median progression-free survival by 10.7 months, although with no demonstrable OS benefit.[24] Additionally, because denosumab is not cleared through the kidneys, it has a better renal safety profile, especially in patients with creatinine clearance of 30—60 ml/min.

Dosing frequency of BTAs. Survival of patients with metastatic cancer has improved over recent decades and patients with oligometastatic disease may survive >10 years after diagnosis of metastatic disease. As survival times increase, concerns about cumulative risks for AEs, treatment costs and inconvenience for patients with prolonged use of BTAs have emerged. There are no prospective data on the validity of intermittent treatments or 'drug holidays', but extended dosing intervals of zoledronate have been tested in several randomised trials.

The ZOOM and OPTIMIZE-2 trials were underpowered for reliable results but suggested noninferiority between 4- and 12-week schedules initiated after 12—15 months of bisphosphonate treatment. In a larger study, patients with either breast cancer, CRPC or MM were randomised at the initiation of bisphosphonate treatment to zoledronate every 12 or every 4 weeks. The proportions of patients experiencing ≥1 SRE were similar (29% in both arms), both overall and in each of the three disease groups studied. However, more patients receiving zoledronate every 12 weeks required bone surgery.[25] The incidence of osteonecrosis of the jaw (ONJ) was low and similar on both schedules.

Overall, the results of these trials suggest similar efficacy with dosing of zoledronate every 12 weeks. However, follow-up is relatively short and results of the largest study suggest the possibility of an increase in serious SREs with the extended treatment schedule and thus an initial monthly treatment for 3—6 months seems prudent.

The pharmacokinetics of denosumab argue against intermittent treatments. Unlike bisphosphonates, with their accumulation in bone and prolonged duration of action, denosumab is not stored in bone and interrupting its administration is probably not without risk. Studies in osteoporosis patients have shown a rapid rebound in bone turnover after denosumab is stopped, associated with an increase in vertebral fractures.[26] It is not known if the same applies to cancer patients treated with denosumab but, based on its pharmacodynamics and systemic distribution, continuous monthly therapy with denosumab should be adhered to until shown otherwise.

Safety of BTAs. Both bisphosphonates and denosumab are generally well tolerated treatments. However, some important AEs can occur and it is important that physicians advise patients on safety issues and implement proactive management to limit their frequency and severity. With the exception of the acute phase response causing fever and myalgias, AEs after administration of i.v. bisphosphonates are infrequent, provided the drug is infused at the recommended dose and duration. Particular attention should be paid to the potential renal toxicity of bisphosphonates, especially in MM. With zoledronate, stepwise dose reductions when baseline creatinine clearance is 30—60 ml/min are advocated and zoledronate is not recommended in patients with creatinine clearance <30 ml/min. In this setting or in those taking nephrotoxic medications, denosumab is the preferred BTA.

With oral agents, oesophagitis, dyspepsia and/or diarrhoea may occur but only occasionally lead to treatment discontinuation.

Calcium balance. Inhibition of bone resorption by BTAs may cause hypocalcaemia. This is most pronounced with the use of denosumab. Calcium levels should be monitored, especially during the first few months of treatment and vitamin D levels assessed before starting treatment.

Vitamin D levels are typically low in cancer patients and those with vitamin D deficiency should have their levels corrected with oral vitamin D3 (25—50 000 IU per week for 4—8 weeks). Vitamin D levels should be maintained with daily supplements (800—2000 IU per day) of vitamin D3. Calcium supplementation may also be required to ensure an adequate daily intake of 1000—1200 mg per day.

Osteonecrosis of the jaw. The most important AE associated with prolonged administration of potent inhibitors of bone resorption is ONJ.[27] The definition, diagnosis and follow-up of ONJ have been described by various societies and expert groups. ONJ is characterised by (usually) painful bone destruction, secondary infection and delayed healing in the mandible and/or maxilla. ONJ is more common when i.v. bisphosphonates or denosumab are administered on a monthly basis for control of metastases and much less frequent with less intensive use of bisphosphonates or denosumab, for example oral bisphosphonates or use of 6-monthly zoledronate or denosumab for prevention of bone loss. The frequency may be higher in MM than in patients with solid tumours and potentiated by the association of BTAs with antiangiogenic drugs.[27] With monthly treatment, the incidence of ONJ is similar for zoledronate and denosumab at about 1% per year on treatment.[28] Most patients developing ONJ will have had tooth extraction and/or poor oral hygiene or use of a dental appliance.

Before BTA therapy is initiated, an oral examination and appropriate preventive dentistry are strongly recommended. Patients should avoid invasive dental procedures (extractions and implants) during therapy if possible,

maintain good oral hygiene and ensure regular dental/oral surgery review. When tooth extraction cannot be avoided, prophylactic antibiotics are advised and the BTA should be suspended until healing of the tooth socket appears complete.

Atypical femoral fractures. Atypical femoral fractures (AFFs) affecting the subtrochanteric region and diaphysis of the femur have been reported in patients taking bisphosphonates or denosumab.[29] AFFs are characterised by unique radiographic (transverse fracture line, periosteal callus formation at the fracture site, little or no comminution) and clinical features (prodromal pain, bilaterality) that resemble stress fractures or reactions. Studies with radiographic review of the fractures consistently report significant associations between AFFs and bisphosphonate use, although the strength of associations and magnitude of effect vary. Bisphosphonates localise in areas where stress fractures develop and suppression of targeted intracortical remodelling at the site of AFFs could impair the processes by which stress fractures normally heal.

The absolute risks of AFFs in patients on bisphosphonates/denosumab are low, ranging from 3.2 to 50 cases per 100 000 person-years. However, long-term use may be associated with higher risk (100 per 100 000 person-years). AFFs appear to be more common in patients who have been exposed to long-term treatment (median 7 years); the risk may decline when treatment is stopped.[29]

Rebound osteolysis after denosumab. In contrast to bisphosphonates, denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation. Data from several studies demonstrate a steep increase in bone turnover markers and a rapid decrease in bone mineral density (BMD) after discontinuation of denosumab.[26] Clinical case series and re-analyses of osteoporosis trials of denosumab have reported multiple vertebral fractures occurring after discontinuation of denosumab, presumably due to the rebound increase in bone resorption.[26] Clinicians and patients should be aware of this potential risk in cancer patients both with and without bone metastases. After stopping denosumab, bisphosphonate therapy should be considered to reduce or prevent the rebound and potential excess risk for vertebral fractures. Currently, the optimal bisphosphonate regimen post-denosumab is unknown but many osteoporosis clinicians use a single 4- or 5-mg treatment of zoledronate.

Recommendations

- The investigation and management of patients with bone metastases/bone lesions should be discussed within a multidisciplinary team with links to all therapeutic modalities of relevance [V, A].
- EBRT remains the treatment of choice for localised moderate to severe bone pain due to bone metastases [I, A].
- A single 8-Gy fraction is recommended for painful uncomplicated bone metastases [I, A].
- Prophylactic antiemetics and dexamethasone to minimise nausea/vomiting and pain flare are recommended [II, B].
- Postoperative RT should follow orthopaedic fixation of a long bone or spinal decompression and/or stabilisation [III, B].
- ^{223}Ra is a valuable treatment option for patients with mCRPC and symptomatic multiple skeletal metastases as the dominant site of disease [I, A].
- Currently, ^{223}Ra should be given as a single agent [with luteinising hormone-releasing hormone (LHRH) analogues] following previous use and/or in combination with a BTA [III, A].
- Structurally significant lesions in a long bone should be evaluated by an orthopaedic surgeon to provide advice on suitability for surgery [IV, A].
- Prophylactic surgery for impending fracture is generally preferred to fixation after fracture [III, B].
- It is recommended to start zoledronate or denosumab in all breast cancer patients with bone metastases, whether they are symptomatic or not [I, A].
- BTAs should be initiated at diagnosis of bone metastasis and considered throughout the course of the disease [III, A].
- Zoledronate or denosumab is recommended in patients with CRPC and bone metastases, whether they are symptomatic or not [I, A].
- Bone treatment, other than to prevent/treat cancer treatment-induced bone loss (CTIBL) or pre-existing osteoporosis is not recommended for ESPC [I, B].
- Zoledronate or denosumab is recommended in patients with advanced lung cancer, renal cancer and other solid tumours with a life expectancy of $\geq$3 months and clinically significant bone metastases [I, B].
- Zoledronate, pamidronate or denosumab should be initiated at diagnosis of MM [I, A].
- Denosumab is the agent of choice in MM patients with renal impairment (creatinine clearance $<$60 ml/min) [I, B].
- Therapy with a bisphosphonate can be interrupted after 2 years in patients in remission [II, B].
- Most patients selected for treatment with zoledronate can de-escalate this agent safely to administration every 12 weeks, preferably after monthly treatment for 3—6 months [I, B].
- Denosumab should be administered every 4 weeks. Extending intervals beyond this frequency cannot currently be recommended [III, D].
- Discontinuation of treatment after an arbitrary duration other than perhaps for those patients with oligometastatic bone disease in disease remission is not recommended [V, D].
- Patients should have a dental evaluation and, when feasible, complete invasive dental treatments before initiating a BTA [III, A].
- Correction of vitamin D deficiency and vitamin D supplementation with adequate intake of calcium throughout treatment to maintain normal serum calcium are recommended [I, A].

- Bisphosphonate treatment (e.g. zoledronate) to suppress rebound osteolysis is recommended if denosumab is discontinued for more than 6 months [III, B].

METASTASIS PREVENTION

Metastasis and tumour dormancy are extraordinarily complex processes. However, it is clear that multiple cell types under the influences of hormones, cytokines, growth factors, hypoxia and cell-to-cell contact are intimately involved in maintaining tumour cells within the bone microenvironment and the subsequent development of metastasis. Treatments that modify the microenvironment, such as adjuvant use of BTAs, provide one approach to influence the metastatic process. Promising results in numerous animal model systems have been seen and many clinical trials, especially in early breast cancer, have been conducted over the past two decades.

Breast cancer

Individual studies of adjuvant BTAs have reported varying results and posed difficulties in interpretation. Several early trials testing daily oral clodronate suggested benefits with fewer bone relapses and improved survival but contrary results were also reported that prevented approval of clodronate as an adjuvant treatment strategy.[30]

A decade ago, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) reported significant benefit from the addition of 6-monthly zoledronate when added to endocrine therapy that included ovarian function suppression (OFS) for premenopausal women with estrogen receptor-positive disease.[30] However, the larger AZURE study, with much broader inclusion criteria and utilising a more intensive treatment regimen with zoledronate, showed no benefit in an intention to treat (ITT) analysis.[30] However, the AZURE study did identify potential benefits in a subgroup of patients who were postmenopausal at the time of study entry and generated the hypothesis that treatment benefits were perhaps restricted to women who had low levels of reproductive hormones due to either natural age-related menopause or OFS.

This hypothesis was investigated by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). A meta-analysis of individual patient data from 18 766 breast cancer patients included in randomised trials of adjuvant bisphosphonates showed that adjuvant bisphosphonates (i.v. zoledronate, daily oral clodronate or daily oral ibandronate specifically) reduced breast cancer recurrences (especially in bone) and breast cancer deaths.[31] However, almost all the benefits were restricted to postmenopausal women or those receiving OFS with clinically important benefits in overall breast cancer recurrence, bone recurrence and breast-cancer-specific mortality. This improvement in breast cancer mortality approximated to the prevention of more than one in six breast cancer deaths at 10 years. Benefits appeared similar across biological subtypes of breast cancer [both with estrogen receptor-positive and -negative, low-, intermediate- and high-grade tumours]. A trial comparing zoledronate with daily oral clodronate or ibandronate showed no difference in disease outcomes.[32] However, there are no randomised trials with oral alendronate or risedronate, as commonly used in the treatment of osteoporosis, to support their use for metastasis prevention.

The disease-modifying effects of denosumab have also been assessed in early breast cancer. The osteoporosis schedule of denosumab was evaluated by the ABCSG in a study primarily aimed at assessing the agent's ability to prevent fractures associated with the use of aromatase inhibitors (AIs).[33] A significant improvement in disease-free survival (DFS) was reported, but the apparent benefits of denosumab were driven more by effects on second non-breast primary cancers and deaths without recurrence than prevention of breast cancer recurrences, effects that seem biologically implausible.

In the larger D-CARE study of women with stage II/III breast cancer, denosumab had no significant effects on either bone metastasis-free survival (BMFS), the study primary end point, DFS or OS, with no suggestion of benefits in the postmenopausal subgroup.[34] The apparent differences between the D-CARE results and those reported by the EBCTCG meta-analysis suggest the benefits of adjuvant bisphosphonates may not simply reflect their primary effects on bone cell function but arise from one or more of their effects on the metastatic process identified in preclinical models.[30]

BTAs have a dual function in the context of early breast cancer: inhibition of metastasis and prevention of treatment-induced bone loss. The former indication should be a primary concern for patients at intermediate to high risk of recurrence. Zoledronate, typically initiated alongside adjuvant ChT and then administered every 6 months, or daily oral ibandronate or clodronate can be considered (Figure 2). The optimum duration of treatment of metastasis prevention is uncertain.

Prostate cancer

Prostate cancer spreads predominantly to bone and provides an ideal clinical setting for the evaluation of bone-targeted treatments. However, studies evaluating the potential role of bisphosphonates in patients with high-risk non-metastatic prostate cancer have shown no impact on disease recurrence or metastasis.[2]

In men with CRPC but no evidence of overt metastases (rising prostate-specific antigen), denosumab significantly increased BMFS by a median of 4.2 months over placebo and delayed time to symptomatic first bone metastases.[35] However, with a 5% incidence of ONJ, these disease benefits were not considered sufficient for regulatory approval.

Other solid tumours

The potential impact of BTAs on the natural history of lung cancer has also been evaluated. Neither zoledronate nor denosumab has any measurable impact on disease recurrence or survival.

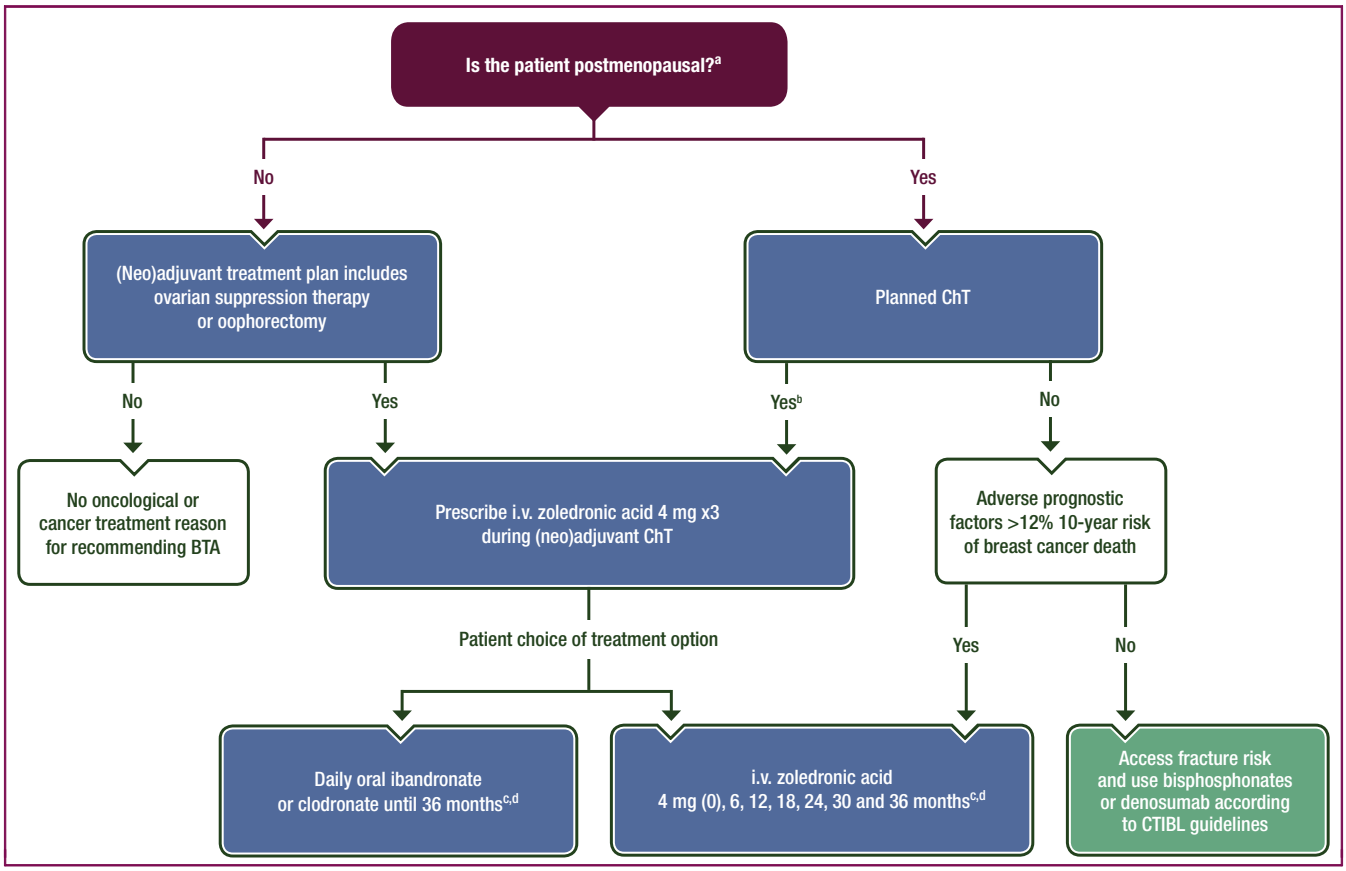

Figure 2. Algorithm for use of bone-targeted treatments in early breast cancer.
BTA, bone-targeted agent; ChT, chemotherapy; CTIBL, cancer treatment-induced bone loss; i.v., intravenous; IUD, intrauterine device; FSH, follicle-stimulating hormone.
[a] If not clinically assessable (i.e. hysterectomy/IUD) then ensure age >55 and/or serum FSH is in postmenopausal range (patient must not be receiving concurrent therapies that can affect the hypophyseal pituitary gonadal axis).
[b] Patients already on weekly oral bisphosphonates for osteoporosis should be considered for a treatment change and follow algorithm.
[c] Include vitamin D3 800–2000 IU (plus calcium 1000 mg daily if low calcium diet).
[d] May switch from oral to i.v. therapy or vice versa if tolerability issues.
Duration of treatment is not well defined and may vary between 2 and 5 years.

Recommendations

- Adjuvant bisphosphonates (i.v. zoledronate or daily oral clodronate or ibandronate) are recommended for postmenopausal women or premenopausal women treated with gonadotropin-releasing hormone (GnRH) analogues with early breast cancer deemed at significant risk for recurrence [I, A].
- Treatment should be initiated alongside (neo)adjuvant ChT (where indicated) and continued for 2–5 years [I, A].
- Bisphosphonates are neither recommended as disease-modifying agents for premenopausal women (not on GnRH analogues) with early breast cancer nor for men or women with other solid tumours [I, E].
- Denosumab is not recommended for the prevention of metastasis [I, D].

CANCER TREATMENT-INDUCED BONE LOSS

Osteoporosis is defined by low bone mass and microarchitectural deterioration in the structural integrity of bone tissue that results in a high risk of fracture. The rate of bone loss increases with age in both women and men and the lifetime risks of a fracture of the hip, spine or distal forearm from age 50 years onwards are 40% and 13% in Caucasian women and men, respectively.[36]

Estrogen deficiency is the major cause of accelerated bone loss. Consequently, estrogen deprivation in women with breast cancer will accelerate bone turnover leading to a decrease in BMD and a 40%–50% increase in fracture incidence.[37] Androgen deprivation therapy (ADT) also suppresses estrogen production and thereby leads to accelerated bone loss and an increase in fracture rate.[38] In premenopausal women, treatments may induce premature menopause or be specifically designed to suppress ovarian function. Cytotoxic ChT may also have direct negative effects on bone metabolism.[39]

Risk factors for osteoporosis-related fractures have been validated in large prospective as well as population-based studies in postmenopausal women but not specifically defined for either women with a history of breast cancer or men with prostate cancer (see Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.07.019). Current fracture risk assessment tools do not adequately address the risks associated with treatments in premenopausal women, especially those aged <35.

Prevention and management of CTIBL

Several guidelines recommend that women with breast cancer receiving an AI or OFS and men with prostate cancer undergoing ADT should be assessed for fracture risk based on clinical risk factors and BMD (Figure 3).[37,38] Premenopausal women should also be informed of the potential risk of bone loss before beginning anticancer therapy.

All patients receiving treatments that are known to adversely affect bone health should be advised to consume a calcium-enriched diet, exercise moderately (resistance and weight-bearing exercise) and take 1000—2000 IU vitamin D3 every day (see Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2020.07.019). If a calcium-enriched diet is not sufficient to ensure the uptake of 1000—1200 mg calcium per day, a supplementation of 500—1000 mg is recommended.

For postmenopausal women or men on ADT, BTAs are recommended if there are ≥2 risk factors for fracture, the BMD T score is <−2 or annual bone loss on treatment is confirmed to exceed 5%.[37,38] Data from multiple RCTs show that administration of bisphosphonates (both i.v. and oral) and denosumab can prevent bone loss in women with breast cancer and men on ADT. Dose schedules similar to those used for the treatment of postmenopausal osteoporosis are sufficient.[37,38]

In postmenopausal women receiving an AI, denosumab 60 mg once every 6 months in addition to adequate calcium and vitamin D supplementation reduced fractures by 50% compared with placebo, providing the best evidence to date for the use of a BTA for preservation of bone health in early breast cancer. This effect was independent of age and BMD at baseline.[33]

Alendronate, risedronate, pamidronate and zoledronate have all been shown to prevent bone loss from ADT in patients with locally advanced prostate cancer.[38] Of these treatments, 6- to 12-monthly zoledronate (4-5 mg) and 6-monthly denosumab (60 mg) are considered the most

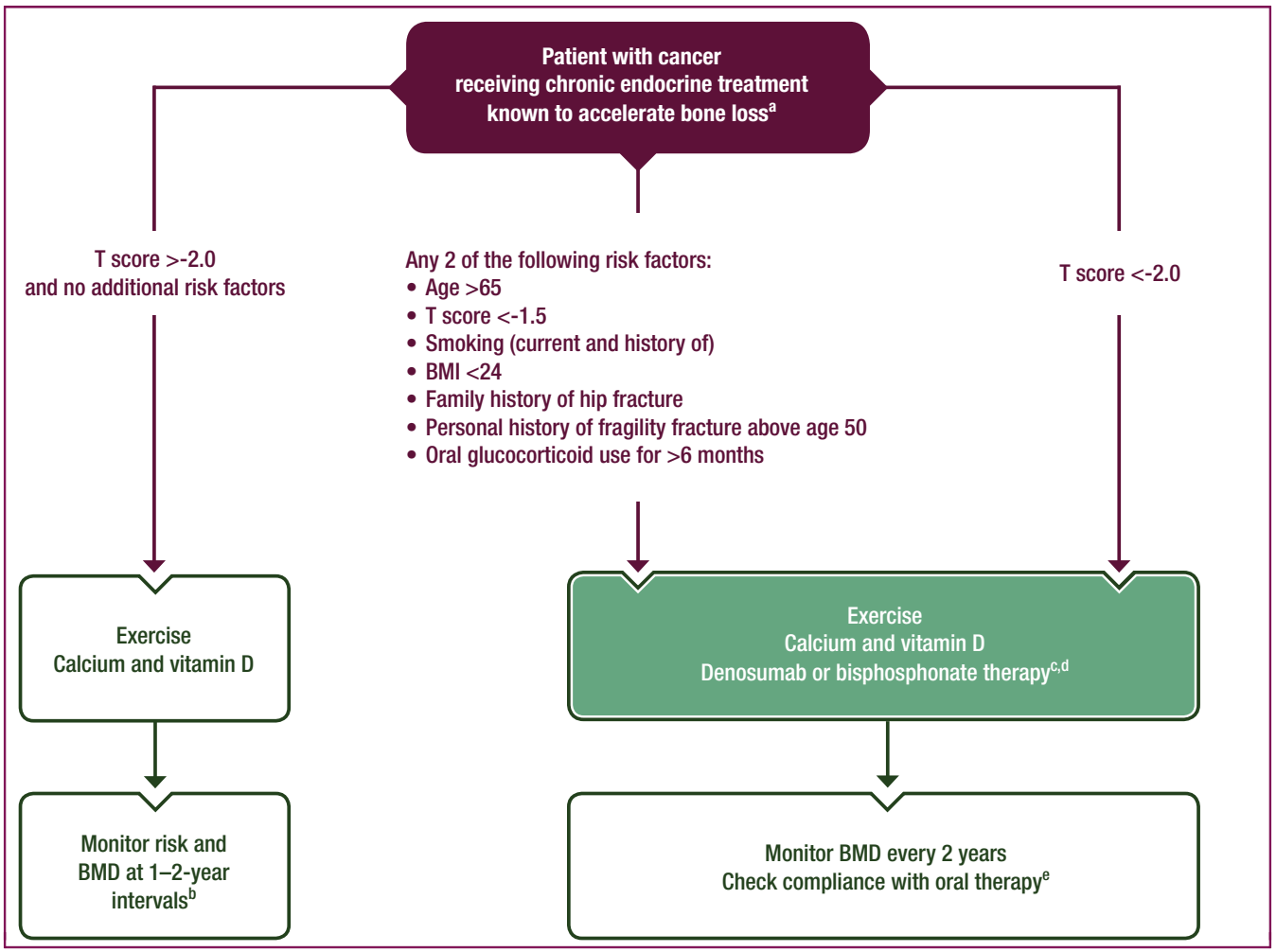

Figure 3. Recommended algorithm for managing bone health during cancer treatment.
ADT, androgen deprivation therapy; AI, aromatase inhibitor; BMD, bone mineral density; BMI, body mass index; DXA, dual X-ray absorptiometry; ONJ, osteonecrosis of the jaw.
[a] Include AIs and ovarian suppression therapy/oophorectomy for breast cancer and ADT for prostate cancer.
[b] If patients experience an annual decrease in BMD of ≥10% (or ≥4%—5% in patients who were osteopenic at baseline) using the same DXA machine, secondary causes of bone loss such as vitamin D deficiency should be evaluated and antiresorptive therapy initiated. Use lowest T score from spine and hip.
[c] Six-monthly intravenous zoledronate, weekly oral alendronate or risedronate or monthly oral ibandronate for the duration of endocrine treatment/for up to 5 years.
[d] Denosumab as first-line treatment followed by bisphosphonates (together for up to 5 years).
[e] Although ONJ is a very rare event with bone protection doses of antiresorptives, regular dental care and attention to oral health is advisable.
Adapted from Hadji et al. 2017[37] under a Creative Commons license. https://www.creativecommons.org/licenses/by-nc-nd/2.0/.

convenient and reliable treatments. However, only denosumab has a specific licence for treatment-induced bone loss associated with ADT. In the placebo-controlled HALT study, denosumab treatment significantly reduced the incidence of new vertebral fractures by 62% and BMD increased from baseline at all sites compared with the placebo group.[40]

Recommendations

- In at-risk patients, an assessment of clinical risk factors and measurement of BMD by dual X-ray absorptiometry is recommended [V, A].
- Weight-bearing exercise, smoking cessation, reduced alcohol intake and vitamin D supplements (and calcium) should be encouraged [I, B].
- Antiresorptive therapy is recommended in women receiving either an AI or OFS and men on ADT for >6 months with either a BMD T score of <-2 or with ≥ 2 risk factors for fracture [I, A].
- Denosumab 60 mg every 6 months is the treatment of choice to prevent fractures in men on ADT and postmenopausal women with early breast cancer at low risk for disease recurrence [I, B].

SPECIAL CONSIDERATIONS

Spinal metastases

Skeletal metastases most frequently occur in the vertebral column. Due to the particular anatomy and biomechanics of the spine, early diagnosis and prompt management of spinal metastases are crucial. The indications for surgery depend on symptoms, imaging findings and the overall prognosis. Besides the preoperative neurological condition and the PS, the biology of the primary tumour and the life expectancy of the patient are key determining factors. When tumour masses and pathological fractures of the vertebra cause compression of the spinal cord and/or nerve roots with neurological deficits or uncontrollable pain, immediate surgical intervention is justified.

Instability of the vertebral body may cause intractable pain and progress to neurological impairment. The Spinal Instability Neoplastic Score (SINS) uses six features of the metastasis to give a score (SINS 0—18), with higher scores indicating the more unstable lesion and need for intervention.

Operative techniques for spinal metastases differ according to the site and size of the metastases. In advanced cancer, a palliative decompression by a posterior approach and spinal instrumentation to restore stability followed by RT are generally recommended. However, if prolonged survival is anticipated due to a slow growing tumour or a relatively good prognosis, more aggressive interventions can be justified including total *en bloc* spondylectomy for solitary lesions.

Pain inflicted by vertebral body fractures can also be treated by percutaneous cement augmentation (vertebroplasty or kyphoplasty). The techniques have comparable efficacy on pain relief (within 1—3 days) and functional outcomes. Additive effects are obtained by combining with RT.

SBRT, cryoablation and radiofrequency ablation (RFA) can also relieve pain from bone metastasis and reduce the tumour burden in bone. Minimally-invasive RFA and vertebroplasty/kyphoplasty are used in combination to reduce tumour mass, create a cavity and stabilise the vertebral body.

SBRT has emerged as an option for the management of spinal metastases, with rates of local tumour control and pain relief $>80\%$.[12] In a randomised phase II trial of SBRT versus three-dimensional conformal RT for spinal metastases, patients who received SBRT had significantly more pain relief at 6 months and achieved pain relief more quickly.[41] QoL, fatigue and emotional distress were similar with both treatment approaches.

Special considerations in the elderly

Despite an increased risk for fracture and increased tendency to fall, BTAs are typically underutilised in the elderly to prevent skeletal morbidity.[42] In addition to preventing SREs in the oncology setting, BTAs are indicated for fracture risk reduction in elderly patients with osteoporosis.[36] Although oral bisphosphonates such as risedronate and alendronate have demonstrated efficacy in the postmenopausal osteoporosis setting, the complex dosing regimen can lead to poor patient compliance. Parenteral agents such as a single annual infusion of zoledronate or 6-monthly denosumab are highly effective and will improve adherence to treatment.[36]

Particular care during treatment with BTAs is needed for elderly patients who may have renal impairment and other comorbid conditions requiring concomitant medications that can increase the risk for AEs.[42]

Recommendations

- Structurally significant lesions in the spine should be evaluated by an orthopaedic/spinal surgeon to provide advice on suitability for surgery [IV, A].
- Vertebroplasty and kyphoplasty are minimally-invasive therapeutic options that should be discussed within the multidisciplinary team [I, B].
- Elderly patients are at increased risk for fracture and are more likely to require pharmacological treatment to prevent CTIBL [III, A].
- Enhanced monitoring for the effects of comorbidities on treatment safety should be followed in the elderly [V, A].

PERSONALISED MEDICINE

BTAs are administered to patients with metastatic bone disease at risk for SREs across all tumour types and are not targeted to a specific phenotype or based on the presence of a biomarker. Bone markers may help identify patients at high risk for SREs or bone lesion progression as well as monitor adherence to BTAs.[10] However, they are not used in routine practice to select patients for treatment.

For metastasis prevention, treatment is restricted to postmenopausal women with breast cancer considered to be at intermediate to high risk of recurrence. Efforts are ongoing to identify biomarkers that may predict benefit (and harm) from manipulation of the bone microenvironment. One such biomarker—*MAF*, a transcription factor that is amplified in around 20% of bone metastases—has been shown in one study to predict disease benefits with zoledronate in those with normal *MAF* status and harm, especially in younger patients and in those with *MAF* amplification.[43] Validation of these results are awaited before this biomarker can be considered for routine use.

For CTIBL, treatment recommendations are based on the risk of fracture, using algorithms that evaluate clinical risk factors and BMD measurements.[36] The World Health Organization Fracture Risk Assessment tool (FRAX) algorithm is valid for both women and men and calculates the 10-year fracture risk with or without BMD measurement.[36] It includes several fracture-related risk factors, although anticancer treatments are not included as a specific risk factor. Treatment with BTAs in patients receiving AI therapy with a T score <-2 or ≥ 2 clinical risk factors for fracture is the consensus recommendation from expert panels.[37,38]

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMOGuidelines-Methodology). The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2020.07.019.[44] Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

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SUPPLEMENTARY DATA

Supplementary references supporting the guidelines can be found within the Supplementary material available at https://doi.org/10.1016/j.annonc.2020.07.019.

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