Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Diagnosis and treatment of prostate cancer-related bone disease

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Bone disease is a major problem for patients suffering from advanced prostate cancer. It can result either from metastatic osseous lesions severely impairing patients' quality of life and overall survival or from androgen deprivation therapy (ADT) and secondary osteopenia osteoporosis associated with an increased risk for skeletal-related events. Activation of osteoclasts is essential for both ADT-induced osteoporosis and metastatic bone disease. The individual risk of developing fractures during ADT can be evaluated by analysis of bone mineral density and fracture risk models. General measures can be recommended to all patients receiving ADT. Bisphosphonates, RANKL inhibitors and selective estrogen receptor modulators are effective tools to reduce bone loss during ADT. Besides imaging, serum and urine markers are gaining increasing importance in diagnosis and follow up of bone metastases. Bisphosphonates are the current standard of bone-targeted treatment for patients with bone metastases. The RANKL inhibitor denosumab has recently been approved for the prevention of skeletal-related events in patients with metastatic bone disease from prostate cancer. Whether bisphosphonates and denosumab can prevent the development of bone metastases is being investigated at present. Endothelin-A receptor antagonists and Src-inhibitors are under investigation for treatment and prevention of bone metastases yielding different effectiveness in initial preliminary clinical trials.

Keywords: androgen deprivation therapy • bisphosphonates • bone metastases • dasatinib • denosumab • osteoporosis • prostate cancer • RANKL • toremifene • treatment-induced bone loss • zibotentan

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Prostate cancer affects bone metabolism in different ways. Nonmetastatic prostate cancer in untreated patients is associated with a lower bone mineral density (BMD) [1]. BMD can also be reduced in patients treated with androgen deprivation therapy (ADT), which can be achieved by pharmacological hormonal manipulation or surgical castration. The reduction of BMD is even more pronounced in patients treated with ADT compared with postmenopausal women [2]. It is associated with a higher incidence of lumbar spine and hip fractures, and therefore, has a significant impact on morbidity and mortality [3–5]. Moreover, in men with hip fractures, the mortality after 1 year reaches up to 38% [6]. On the other hand, the risk of additional skeletal-related events (SREs), that is, pain, compression of the spinal cord or metabolic disturbances such as hypercalcemia (which is more common in other malignancies with lytic or mixed bone lesions) is also increased in the presence of metastatic bone disease [7,8]. Metastatic bone disease and ADT-induced bone loss can both lead to loss of mobility, decrease in quality of life [9,10] and a significant increase in medical costs [10]. This article reviews current trends and future perspectives in pathophysiology, diagnosis and treatment

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(including options already approved for therapy and options currently investigated in clinical trials) of both ADT-induced osteoporosis and bone metastases from prostate cancer.

Pathophysiology of ADT-induced osteoporosis

Besides chronic glucocorticoid therapy, alcoholism and smoking, hypogonadism is one of the most frequent causes of acquired osteoporosis in men [11]. ADT for prostate cancer has been shown to increase bone turnover [12] by increasing sensitivity of osteoclasts to parathyroid hormone (PTH) [13]. Androgens are also able to inhibit the release of RANKL, which is an important mediator of osteoclast activation [14]. Furthermore, androgens influence the release of IL-6 that regulates bone resorption [15]. Thus, ADT may subsequently lead to increased activation of RANKL and osteoclasts. An important mechanism of osteoporosis during ADT is therapy-induced estrogen deficiency [16]. Estrogens directly influence bone metabolism by interacting with estrogen receptors on osteoblasts and osteoclasts [17]. They regulate the release of growth factors and cytokines by immune cells that attenuate osteoblast and osteoclast activation and are, therefore, important determinants of bone metabolism [18,19].

The normal range of bone loss is 0.5–1.0% per year and occurs from mid-life [20]. During the initial phase of ADT, patients sustain loss in BMD of the hip and spine of approximately 2–3% per year [21]. Interestingly, in patients who underwent bilateral orchiectomy, a loss of BMD of the hip of 9.6%/year has been reported. The decrease of BMD is evident for up to 10 years during ADT and most distinctive during the first year of treatment [22]. The loss of BMD goes along with an increased risk of clinical fractures in patients treated with gonadotropin releasing hormone (GnRH) agonists. Moreover, duration of treatment directly correlates with risk of developing fractures [3], and treatment with GnRH agonists was shown to independently predict fracture risk [23]. Whether newer drugs inhibiting hormonal pathways also influence bone metabolism, has to be evaluated in clinical trials. One of these drugs, which are currently investigated in clinical trials in patients with castration-resistant prostate cancer (CRPC), is abiraterone. It is a specific inhibitor of the enzyme CYP17A1, which is essential for testosterone production in the testes, prostate and adrenal gland. As CYP17A1 is also involved in estrogen production, abiraterone leads to a decrease of testosterone and estrogen levels without causing adrenal insufficiency. First results from recent clinical trials available show promising effects of abiraterone in patients with CRPC [24]. So far, there is not enough clinical data to evaluate its effect on BMD and fracture risk.

Besides ADT-induced osteoporosis, bone metabolism and skeletal stability are also impaired by glucocorticoids. These drugs are widely used in patients with prostate cancer especially during chemotherapy with the objective to increase the efficacy of the chemotherapeutic drugs. The chronic intake of glucocorticoids is a well-known risk factor for development of osteoporosis.

Pathophysiology of metastatic bone disease

It has been estimated that more than 80% of men who die with prostate cancer develop bone metastases [25]. The median time between the clinical diagnosis of metastatic bone disease and death is 3–5 years [26]. Although metastatic bone disease from prostate cancer features mostly osteoblastic characteristics, bone formation and resorption are dysregulated both ways [27]. This osseous metastatic tissue is less stable than the normal bone and is associated with an increased risk of fracture [28].

The process of formation of bone metastases involves several steps. First, the metastatic tumor cell spread occurs from the primary tumor site. After survival in blood circulation, tumor cells bind to the endothelial cells of the bone marrow and establish a conducive microenvironment via crosstalk with osteoblasts and osteoclasts leading finally to a proliferation of tumor cells. On the one hand, tumor cells secrete cytokines (e.g., PTH-related peptide [PTHrP] and TGF-β) that stimulate osteoclasts and lead to the release of growth factors from the osseous tissue. On the other hand, tumor cells activate osteoblasts by releasing osteoblastic factors such as VEGF, PDGF and endothelin-1 (ET-1) [29–31]. Physical factors in the bone microenvironment, such as hypoxia and acidic pH, contribute to the release of osteolytic and osteoblastic factors from tumor cells [32].

Paget's theory suggests that both host response and tumor activity are relevant for the development of bone metastases [33]. The growth of metastases in the bone is assumed to be promoted by growth factors secreted by the host and tumor cells which proliferate in the bone and bone marrow. Prostate cancer cells tend to infiltrate most frequently the trabecular bone of the axial skeleton (e.g., lumbar spine and pelvis) as well as the proximal ends of the femur. The cause for this phenomenon may be due to interaction between the Batson plexus, which forms a network of veins and receives blood from the prostate, and the marrow spaces of the vertebral column [34]. Evidence supporting the theory of hematogenic spread is based on the detection of circulating tumor cells before clinical detection of bone metastases [35,36]. Once tumor cells enter the bone marrow, they bind to the endothelium and finally migrate into the bone microenvironment [37–39]. Disseminated tumor cells can be detected in the bone marrow of patients without clinical evidence of metastases. The presence of disseminated

tumor cells has been demonstrated to be a prognostic factor [40,41]. Tumor cells can interact with bone marrow microenvironment and lead to an activation of local bone resorption by osteoclasts [42]. Osteoclastogenesis is regulated by the RANKL [43]. RANKL is secreted by osteoblast precursor cells and stromal cells [27]. This secretion is promoted by several factors produced by tumor cells such as PTHrP [27]. RANKL binds to the RANK receptor on preosteoclasts and stimulates osteoclastogenesis with subsequent bone resorption [44]. Bone resorption drives the release of growth factors including IGFs, FGFs, TGF-β, PDGF and bone morphogenetic proteins (BMPs). These growth factors promote, in turn, the proliferation of tumor cells and the release of factors stimulating osteoclasts (e.g., PTHrP and IL-6) and osteoblasts (e.g., VEGF and PDGF) [27,32,45]. This whole process displays a vicious cycle of bone destruction in metastatic bone disease (Figure 1).

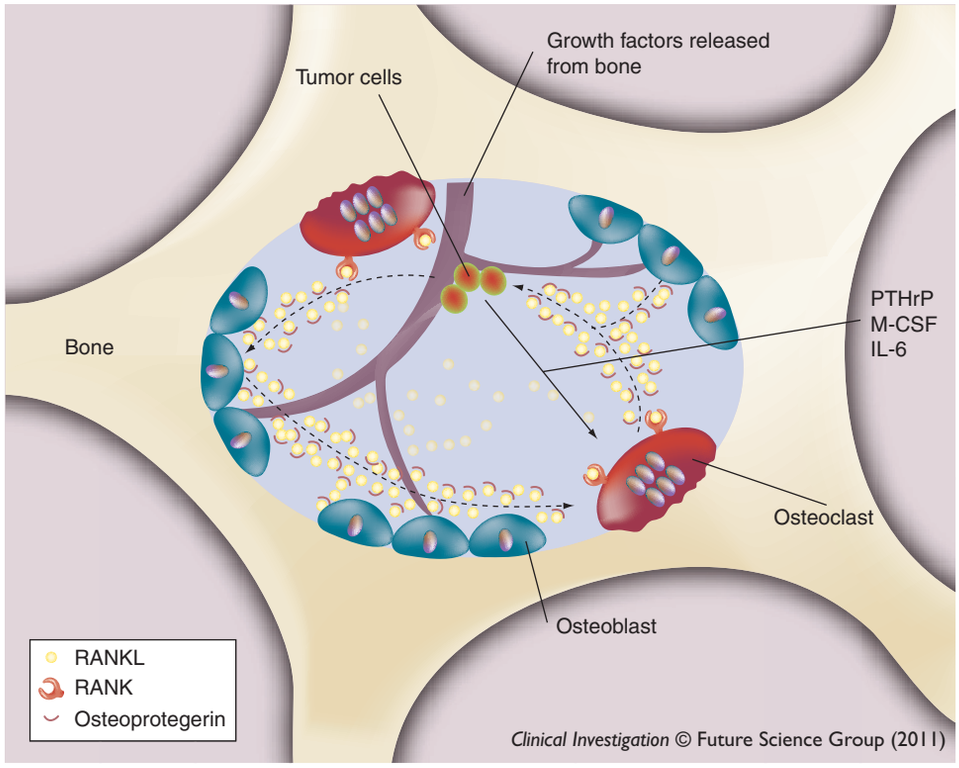

Figure 1. Pathophysiology of metastatic bone disease. Tumor cells secrete factors such as PTHrP, M-CSF and IL-6 that promote the activation of osteoclasts. Tumor cells induce the release of RANKL from osteoblasts. RANKL binds on RANK and activates osteoclasts. Osteoprotegerin produced by osteoblasts binds and inactivates RANKL. Bone resorption by osteoclasts releases factors such as IGF, FGF, PDGF and bone morphogenic proteins. These factors stimulate the proliferation of tumor cells.
M-CSF: Macrophage colony stimulating factor; PTHrP: Parathyroid-hormone-related peptide; RANKL: RANK ligand.

Diagnosis of ADT-induced bone loss

As iatrogenic hypogonadism induces decreased BMD, patients who undergo ADT have to be evaluated concerning their risk of developing fractures. It is essential to assess other risk factors of osteoporosis. These include age of over 65 years, previous fractures, family history of osteoporosis, low BMD, corticosteroid use, alcohol consumption, previous fractures and ADT longer than 6 months [46]. A further important step is to determine the baseline BMD before therapy with repeated measurements during therapy. Since bone loss is most significant in the first year of therapy [22], measurement of BMD can be repeated within 12 months. There are several techniques to determine BMD. The standard method is dual-energy x-ray absorptiometry (DXA). This method is based on two x-ray beams with different energy levels that measure a 2D area of BMD [47]. The diagnosis of osteoporosis is confirmed if BMD is less than or equal to 2.5 standard deviations below the value of a young adult reference population. This is expressed as the so-called 'T-score' [48]. The indication to perform DXA depends on the type of fracture that needs to be predicted. For instance, the risk of developing hip fractures is most accurately predictable by the measurement of BMD of the femoral neck. Therefore, guidelines propose DXA of the femoral neck and lumbar spine as most osteoporotic fractures occur in the hip or spine region.

An alternative technique, which is used increasingly for analyzing BMD, is quantitative computed tomography (QCT). In contrast to DXA, QCT is not size dependent and allows separate measurement of the cortical and trabecular BMD [49]. QCT of the spine and femoral neck has been shown to be at least as accurate as DXA in predicting the risk of fracture development [50–52]. Limitations of QCT include a relatively high level of ionizing irradiation compared with DXA [53] and scarce data compared with DXA, especially for its use in children and men. Peripheral quantitative computed tomography as an alternative to QCT (pQCT) shows negligible doses of radiation exposure and has shown improved accuracy in predicting fractures [54]. However, to date, DXA remains the most widespread technique to measure BMD.

The fracture risk model developed by Kanis *et al.* is a tool to predict the risk of fracture in men and women, as the measurement of BMD alone might not be sufficient enough to estimate fracture risk [55]. The guidelines of the National Osteoporosis Foundation (NOF) recommend initiating a treatment at the age of at least 50 years in men with low BMD (T-score -1 to -2.5, osteopenia) at the femoral neck, total hip, or spine and with 10-year risk probability of at least 3% of hip fracture or a 10-year major osteoporosis-related fracture probability of at least 20% based on the US-adapted WHO absolute fracture risk model [56,57]. However, the fracture risk assessment model has not been properly validated in patients treated with ADT. Furthermore, both fracture risk models and BMD measurement can be confounded by sclerotic metastases.

Diagnosis of bone metastases

In patients newly diagnosed with prostate cancer, serum prostate specific antigen (PSA) can help to determine the necessity for further imaging. A pretreatment PSA above 100 ng/ml has been demonstrated to be associated with a positive predictive value of 100% for the presence of bone metastases [58]. On the contrary, asymptomatic patients with a well or moderate differentiated tumor and a PSA below 20 ng/ml have a very low probability of bone metastasis and, therefore, do not require routine radiological work-up [59]. The 2010 EAU guidelines recommend radiological investigations for bone metastases only in patients with symptoms suspicious of bone metastases, poorly differentiated tumors and in those with well or moderately differentiated tumors with a PSA of at least 20 ng/ml [60]. For asymptomatic patients who underwent primary therapy with intent to cure or patients undergoing ADT, the absolute PSA value and PSA velocity have to be considered for the decision making of performing radiological investigations [61–63]. The accuracy of predicting bone metastases can be improved up to 98%, when PSA and bone-specific alkaline phosphatase (BAP) are determined in the serum [64]. Patients who are at risk for bone disease are recommended to undergo radiologic investigation.

Imaging of bone metastases

Radiological imaging of bone metastases is essential for correct diagnosis and evaluation of treatment response. For evaluation of treatment response to sytemic therapy, it has to be considered, that in contrast to other malignancies, the radiological evaluation criteria in solid tumors (RECIST) should not be used in most osseous lesions of prostate cancer patients [65] since only mixed osteolytic osteoblastic or pure osteolytic lesions can be measured reliably with this method.

When selecting the appropriate imaging technique to evaluate bone metastases, it has to be considered that different techniques visualize different tumor characteristics. X-ray, CT and MRI are able to detect structural changes of bone and bone marrow, whereas functional techniques like skeletal scintigraphy, PET and single photon emission computed tomography (SPECT) measure metabolism of bone and tumor cells. Newer hybrid techniques like PET/CT are capable to detect changes both in bone structure and metabolism. In the following section, imaging techniques are reviewed with regard to their ability to detect metastases and evaluate treatment response.

Conventional x-ray

X-ray is often used for clarifying nonspecific or atypical findings in skeletal scintigraphy. It is able to detect structural changes of the bone like osteolysis or osteosclerosis. In prostate cancer, sclerotic lesions are predominantly found. X-ray can only detect lesions with a loss of bone mineral content exceeding 50% [66]. It could be shown, that it has a much lower sensitivity in detecting bone metastases than skeletal scintigraphy [67]. Its low spatial resolution and superposition of structures result in a high rate of equivocal evaluations. Response to treatment does not become apparent 3–6 months after initiation of therapy [68].

CT

In contrast to x-ray, CT as a whole body imaging technique shows a higher resolution of anatomical details. It is able to detect metastatic spread earlier than x-ray in the bone marrow before bone destruction becomes clinically apparent [69]. Its sensitivity ranges from 71–100% [67]. Compared to x-ray, CT is also superior for the assessment of treatment response [70]. Besides MRI, CT is the only technique that is recommended in the revised RECIST guidelines for the measurement of osteolytic or mixed osteolytic-osteoblastic lesions [65]. This demonstrates its superiority compared with functional imaging techniques in evaluating treatment response. One of the most important applications of CT is the evaluation of skeletal stability and fracture risk turning it into an important diagnostic tool in patients with bone metastases.

MRI

Magnetic resonance imaging is superior to CT in detecting bone marrow lesions and extraosseous growth of bone metastases as it has a higher soft tissue contrast [71]. Compared to skeletal scintigraphy, MRI has an improved sensitivity and specificity. This provides higher detection rates [72] and improved visualization of bone metastases in patients with negative

bone scan findings [73]. This discrepancy arises from the fact that even in the case of extensive bone marrow involvement the amount of destroyed bone matrix is little [74]. MRI has been shown to be appropriate in order to assess treatment response due to excellent soft tissue contrast. It facilitates the evaluation of changes in tumor size and differentiation between viable tumor and necrosis. Tombal *et al.* demonstrated that MRI is able to quantitatively measure treatment response on the basis of the RECIST criteria in single bone lesions [75].

Diffusion weighted imaging (DWI) is a novel technique allowing for better quantitative assessment of tumor growth. Based on its principle of visualization of changes in the motion of water molecules it is capable of detecting tumors and post-treatment tissue changes [76]. Quantitative DWI has been demonstrated to predict the tumor response to chemotherapy and visualize treatment-related intratumoral tissue changes before changes in tumor growth become apparent [77–80]. While these results indicate that DWI can be a valuable additional tool for the evaluation of treatment response, the advantages in the diagnosis of bone metastases compared with skeletal scintigraphy is discussed controversially in current literature [81,82].

Bone scintigraphy

Tcm99-MDP-scintigraphy is still the gold standard technique for detecting bone metastases in patients with prostate cancer. The extent of disease can be evaluated by a semi-quantitative grading system, which has been shown to correlate with overall survival in patients with prostate cancer [83]. Bone scintigraphy detects bone metastases up to 18 months earlier than plain x-ray. One of its limitations is its low sensitivity and specificity compared with MRI for the detection of bone metastases at an earlier stage of the disease. Compared to other techniques, it provides a higher number of equivocal reports. Bone scintigraphy is also limited by providing less quantitative information, which is especially needed in evaluating treatment response. One attempt to quantitatively analyze bone metastases but has not been widely adopted so far is the bone scan index, which was described by Imbriaco *et al.* [84]. Detectable response on bone scan is often delayed up to 6–8 months [85]. An important limitation for the evaluation of treatment response is the flare-up phenomenon that can be detected up to 6 months after induction of systemic therapy and hampers the differentiation between response and disease progression [86]. Owing to its high availability and profound clinical data, bone scintigraphy is nowadays still the method of choice for the detection bone metastases.

PET

PET is another technique to visualize tumor cell metabolism. Fluorodeoxyglucose (FDG) is the tracer most commonly used for the detection of tumor cell metabolism. As its uptake is elevated in all cells with high glucose metabolism (i.e., muscle tissue, inflammation, blood system) unspecific FDG uptake can limit the detection of bone metastases [87]. Compared to bone scintigraphy, FDG PET alone shows decreased sensitivity and specificity for the detection of sclerotic bone metastases [88]. However, FDG PET could be identified as a promising outcome parameter for patients with CRPC [89]. Alternatively, F-fluoride is a more specific bone PET tracer representing osteoblastic activity with a high sensitivity for the detection of bone metastases owing to its high imaging contrast between normal and abnormal bone tissue [90–92].

Hybrid techniques

The inability of PET to visualize structural changes and its low spatial resolution led to the development of novel hybrid techniques such as PET/CT and PET/MRI. Both techniques combine functional and structural data and show better results than PET and CT alone. Additionally, they are superior to bone scintigraphy in the detection of bone metastases [91,93,94]. The positive predictive value for the detection of bone lesions with both techniques is approximately 98% [94] and several studies have demonstrated that information acquired from both techniques are complementary. Other fusion techniques such as SPECT/CT have also been used to detect bone metastases with a high sensitivity and specificity, and with regard to their ability to reduce the rate of equivocal reports examined by bone scintigraphy [95]. However, the main limitation of hybrid techniques is their costs.

Bone turnover markers

To reduce exposition to ionizing radiation and costs, serum and urine markers for diagnosis and follow-up of patients with bone metastases have been studied within the last decade. Serum markers include BAP, cross-linked C-terminal (Ctx) and cross-linked N-terminal (Ntx) telopeptides of type I collagen (which can be also used as a marker in the urine), cross-linked carboxyterminal telopeptide of type I collagen, and N-terminal propeptides of type I procollagen. These markers have been shown to be elevated in patients with bone metastases [96–99]. Furthermore, a correlation between serum markers and extent of disease has been confirmed [100]. There is also evidence that suggests a correlation between the level of bone turnover markers and the risk for SREs, disease progression and death [101–103]. Besides their diagnostic value, bone turnover markers may also be used for marker-directed therapy. Lipton *et al.* demonstrated

that normalization of bone turnover markers is associated with a lower risk of SREs and improved overall survival [104]. Marker levels correlate with response to zoledronic acid [104–106], denosumab [107] and other bone-targeted drugs [108] and are, therefore, used to compare drugs in their ability to reduce bone turnover in clinical studies [109]. We evaluated serum samples from 80 patients with histologically proven prostate cancer, 41 of those with and 39 without bone metastases, and 51 patients with benign prostate hyperplasia for ICTP and PINP [110]. Therapeutic response to bisphosphonate therapy was monitored in seven out of the 41 metastasized patients, 5 and 9 weeks after initiation of therapy. The results demonstrated that both markers for bone turnover were increased in patients with skeletal metastases compared with patients without metastases and to the benign prostate hyperplasia patients. The differences were statistically significant. In patients on bisphosphonate therapy the serum levels decreased significantly.

Bone turnover markers are promising tools to diagnose bone metastasis, support indication for therapy and evaluate treatment response. These characteristics led to the initiation of the BISMARK trial [201] that assesses the potential of urinary Ntx levels to reduce the dose-dependent toxicity of zoledronic acid without impaired oncological efficacy. The trial is already closed and the results are awaited in the near future.

Whenever discussing the role of serum markers for the diagnosis of bone metastases, it has to be borne in mind that ADT-related bone loss also causes an increase in bone turnover markers both in the serum and urine. ADT might, therefore, interfere with changes of bone metabolism due to metastatic disease [111]. Notwithstanding, there is evidence that demonstrates superiority of bone tumor markers to bone scintigraphy in detecting bone metastases regardless of the possible confounding role of ADT [100]. However, one limitation for the routine use of serum bone turnover markers is the possible increase in patients with decreased renal function [112] and the variability of urine markers due to analytic and biologic factors [113]. The large inter-individual variation in bone marker levels also reduces their routine use in clinical practice. An urgent issue that has to be addressed in future trials is to determine the most useful marker for routine clinical use as the variability of markers used in clinical studies make it difficult to compare results. More clinical studies should certainly be conducted to evaluate their significance in metastatic prostate cancer.

Strategies for the treatment of ADT-induced bone loss

When osteoporosis with an increased fracture risk is diagnosed in patients who are treated or planned for treatment with GnRH agonists, it has to be decided whether supportive therapy is required. As mentioned previously, this decision can be made on the basis of models to calculate fracture risk, BMD or the level of bone turnover markers. There are general measures to reduce fracture risk, which can be recommended to all patients receiving ADT. These recommendations include the cessation of smoking [114] and alcohol consumption [115], and initiation of resistance exercise training [116,117]. Another measure, which can be recommended to all patients undergoing hormone ablation therapy, is a dietary intake of calcium and vitamin D that has been shown to reduce bone loss and to decrease fracture risk [118]. Various medicamentous treatment options for ADT-induced osteoporosis are summarized in Table 1 (for levels and corresponding types of evidence see Table 2).

Bisphosphonates

The role of bisphosphonates as a treatment modality to prevent bone loss in patients with ADT-induced osteoporosis has been investigated in a couple of studies. As pyrophosphate analogs, bisphosphonates are internalized by osteoclasts. Nitrogenous bisphosphonates (e.g., zoledronic acid) inhibit the mevalonate pathway, which finally leads to the induction of apoptosis in osteoclasts [119]. Non-nitrogenous bisphosphonates (e.g., clodronate) are metabolized to toxic ATP-analogs. Bisphosphonates that are approved by the US FDA for the treatment of noncancer-associated osteoporosis include alendronate, risedronate, ibandronate and zoledronic acid.

In patients with decreased testosterone levels, alendronate has been shown to increase BMD [120]. In osteopenic patients receiving antihormonal therapy for prostate cancer, alendronate achieved a significant increase in BMD of the lumbar spine and femoral neck [121]. Alendronate as a oral bisphosphonate is associated with major gastrointestinal side effects [122], which lead to a decreased clinical use of this drug. Intravenous bisphosphonates have the advantage that they have to be administered only every 1–12 months. Moreover, in several studies it has been proven that they prevent ADT-related bone loss. In two randomized clinical trials, pamidronate administered during ADT led to a significant reduction or elimination of BMD loss in patients with metastatic or nonmetastatic prostate cancer [123,124]. Zoledronic acid (zoledronate), a more potent intravenous bisphosphonate, has even been shown to increase BMD in patients with nonmetastatic prostate cancer undergoing ADT [22,125]. However, none of the bisphosphonates have ever been proven to reduce the rate of SREs in patients with iatrogenic hypogonadism in a randomized trial. The positive trials performed in patients with ADT-induced bone loss only showed a significant improvement of BMD as a surrogate parameter of fracture risk.

Despite improved gastrointestinal tolerance compared with oral bisphosphonates, zoledronic acid and pamidronate have some major side effects. These include decreased renal function (which may occur during therapy with i.v. bisphosphonates, especially when administered too rapidly or in a very large dose) and osteonecrosis of the jaw (ONJ), which represents a severe side effect. However, its incidence is approximately 5% but is controversially discussed [126]. It occurs mainly during treatment with i.v. zoledronic acid in the context of malignancy. ONJ is difficult to treat and can be cured in only a third of cases [127]. Risk factors are chronic or iatrogenic immune suppression, soft-tissue or bone wounds, i.v. administration of bisphosphonates and duration of treatment. As many side effects of bisphosphonates are dose dependent, it is currently investigated in the BISMARK trial [201] whether the dose of zoledronate can be adapted to the levels of bone resorption markers and, thus, obtain lower rates of side effects without impaired oncological efficacy.

Denosumab

The inhibition of RANKL as a main inductor of osteoclast activity in osteoporosis and cancer-related bone disease has been intensively investigated during the last few years. Various preclinical studies have provided evidence for the major role of RANKL in the process of bone loss [128,129]. Denosumab is a fully human monoclonal antibody targeting RANKL. It has shown to be efficacious for the treatment of postmenopausal osteoporosis in women. In a randomized multicenter Phase III trial (n = 7868), denosumab significantly reduced the incidence of fractures in postmenopausal women [130]. As a result of this study, the FDA and the EMA approved denosumab for therapy of postmenopausal osteoporosis in 2010 for women with an increased risk for fractures. Furthermore, denosumab is an effective tool for the treatment of ADT-induced osteoporosis. In a double-blind, multicenter Phase III study, denosumab was evaluated for its effects on incidence of fractures (primary end point) and the surrogate marker BMD in men with nonmetastatic prostate cancer receiving antihormonal therapy (n = 1468). Denosumab at a dose of 60 mg every 6 months (subcutaneously) significantly increased BMD of lumbar spine, total hip, femoral neck and radius and was the first drug that led to a significantly decreased incidence of new vertebral fractures (3-year incidence of new vertebral fractures 1.5% in the denosumab arm vs 3.9% in the placebo arm; relative risk 0.38; p = 0.006) [131]. Therefore, the EMA approved denosumab for the therapy of ADT-induced osteoporosis in 2010. In this trial denosumab was well tolerated with rates of

Table 1. Strategies for the treatment of androgen-deprivation therapy-induced osteoporosis.

Molecular target	Drug	Results from clinical trials (with patients receiving ADT)	Ongoing clinical trials	Relevant approval status
Mevalonate pathway (AL, ZA, PA) Energy metabolism (CL)	Bisphosphonates (AL, ZA, PA, CL)	Reduction of BMD loss (AL+ PA + ZA + CL), LOE: 1b [121,123–125] Increase of BMD (ZA + AL), LOE: 1b [121,125]	Zoledronic acid to prevent bone loss during ADT (recruitment finished) [210] Zoledronic acid to prevent osteoporosis and bone fractures in patients with locally advanced PC undergoing radiation or ADT (recruitment finished) [211] Zoledronic acid vs placebo to reduce SRE during ADT for patients with bone metastases [202]	Various bisphosphonates are approved for treatment of noncancer-associated osteoporosis by the US FDA and EMA
RANK ligand	Denosumab	Increase of BMD, LOE: 1b [131] Reduced incidence of new vertebral fractures, LOE: 1b [131]	Denosumab for the treatment of bone loss during ADT for nonmetastatic PC (recruitment finished) [212]	Approved for therapy of ADT-induced osteoporosis (EMA)
Estrogen receptor	Toremifene (SERM)	Increase of BMD, LOE: 1b [137] Reduced incidence of new vertebral fractures, LOE: 1b [137]		New drug application for toremifene as treatment option for ADT-induced osteoporosis is awaited in near future

For LOE, see Table 2.

ADT: Androgen deprivation therapy; AL: Alendronate; BMD: Bone mineral density; CL: Clodronate; EMA: European Medicines Agency; LOE: Level of evidence; PA: Pamidronate; PC: Prostate cancer; SERM: Selective estrogen receptor modulator; SRE: Skeletal-related event; ZA: Zoledronic acid.

Table 2. Levels and corresponding types of evidence.

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomization
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Adapted from [214].

adverse events similar the placebo group. Nevertheless, denosumab can also cause ONJ and hypocalcemia [132]. Furthermore, an increased rate of infections was observed in several studies, which emphasizes the important role of the RANKL pathway for immunologic processes [133].

Selective estrogen receptor modulators

As estrogens show a protective effect on bone structure, selective estrogen modulators deliver a popular tool for the treatment of osteoporosis. In men with nonmetastatic prostate cancer treated with GnRH agonists, raloxifene, which acts as an agonist on estrogen receptors in bone tissue and an antagonist in breast and endometrium tissue, could achieve an increase of BMD in the hip by 1.1 ± 0.4% (Phase II study, n = 48) [134–136]. In a recently published Phase III trial with 1284 patients receiving ADT, application of toremifene, another selective estrogen receptor modulator, during a 2-year period resulted in a significantly decreased incidence of new vertebral fractures versus placebo (2-year incidence of new vertebral fractures: 2.5% in the toremifene and 4.9% in the placebo group, relative risk reduction of 50%, p = 0.05) [137]. A significant reduction of bone turnover markers and improvement of BMD as secondary end points could also be confirmed in this study. Thus, toremifene is the second drug after denosumab that could prove a reduction of the fracture rate in patients receiving antihormonal therapy for prostate cancer. An additive positive effect of toremifene is the improvement of lipid profiles in men receiving ADT [137,138]. Cholesterol and triglycerides are increased in patients receiving ADT leading to an increased risk of cardiovascular disease. However, venous thromboembolic events, a well-known problem of therapy with estrogens, occurred more frequently in the toremifene group (2.6 vs 1.1%). It is expected that a new drug application for toremifene in the treatment of ADT-induced osteoporosis will be submitted to the FDA soon.

Bone-relevant strategies for the treatment of osseous metastases of prostate cancer

Beside the drugs used for the inhibition of tumor growth such as GnRH-agonists, antiandrogens and chemotherapeutics, various drugs influencing bone metabolism are available for the treatment of bone metastases in prostate cancer. These drugs will be subsequently reviewed and are summarized in Table 3 (for levels and corresponding types of evidence see Table 2).

■ Bisphosphonates

Bisphosphonates are the standard bone-targeting drug for the treatment of symptomatic bone metastases in cancer patients [139].

Zoledronic acid is the only bisphosphonate approved by the FDA for the treatment of patients with CRPC and metastatic bone disease. In these patients, approval was obtained after zoledronic acid had demonstrated in a large Phase III (n = 643) trial its ability to significantly reduce the rate of SREs (i.e., compression of the spinal cord and fractures) [140].

In this study, patients with CRPC who received ADT and suffered from bone metastases were either treated with zoledronic acid 4 or 8 mg or placebo every 3 months. The study protocol was modified during the trial since nephrotoxicity was observed in some patients and, therefore, the 8 mg dose had to be reduced to 4 mg. The zoledronic acid group arm had a significantly lower rate of SREs (33.2 vs 44.2%, p = 0.021) and a prolonged time to first SRE and showed significantly lower levels of bone resorption markers (70–80%) indicating inhibition of active osteolysis by the drug. As many patients were likely to have entered the trial with general bone loss caused by increased age or previous antihormonal therapy, it is unknown whether the effects of zoledronic acid in this study are the result of an antiosteoporotic effect on the general skeleton or on bone metastases. Overall survival (OS) was not significantly different between the zoledronic acid and placebo arms. Nevertheless, a trend towards improved survival was observed [140].

Table 3. Bone-relevant strategies for the treatment of bone metastases in prostate cancer.

Molecular target	Drug	Results from clinical trials in prostate cancer	Important ongoing clinical trials with primary end point	Approval status
Mevalonate pathway (nitrogenous) Energy metabolism (non-nitrogenous)	Bisphosphonates: ZA, PA, CL	Reduced incidence of SREs (ZA) in patients with CRPC and bone metastases, LOE: 1b [140] Reduction of bone turnover markers (ZA + PA), LOE: 1b [141] Improved overall survival in patients with hormone-sensitive PC and bone metastases (CL), LOE: 1b [144]	ZA vs Placebo during ADT to reduce incidence of SREs; primary end point: time to first SRE [202] ZA to prevent bone metastases in nonmetastatic PC (recruitment finished); primary end point: time to occurrence of first bone metastasis [203] Normal schedule ZA vs marker directed dosage in metastatic breast cancer; primary end point: incidence of SREs [201] ADT alone vs ADT in varying combinations with zoledronate, docetaxel, prednisolone, and celecoxib in patients with locally advanced or metastatic prostate cancer; primary end point: overall survival [204]	ZA is approved by the US FDA and EMA for the treatment of patients with CRPC and bone metastases
RANK ligand	Denosumab	Normalization of bone turnover markers in PC with bone metastases, LOE: 1b [150] Delayed time to first SRE in CRPC with bone metastases (interim results from NCT00321620), LOE: 1b [152]	Denosumab to prevent bone metastases free survival in CRPC (recruitment finished) [205] Denosumab vs ZA in treatment of metastatic CRPC; primary end point: time to first on-study SRE (recruitment finished) [213]	Approved by the FDA for the prevention of SREs in patients with bone metastases from solid tumors
Src	Dasatinib	Normalization of bone turnover markers in metastatic CRPC, LOE: 2b [108] Lack of disease progression, LOE: 2b [108]	Overall survival of patients with metastatic CRPC receiving docetaxel + dasatinib or docetaxel + placebo; primary end point: overall survival [206]	No approval for PC treatment
Endothelin-A receptor	Atrasentan Zibotentan	Slower increases of BAP and PSA in patients with metastatic and nonmetastatic CRPC, LOE: 1b [165] No overall survival benefit in patients with metastatic CRPC, LOE: 1b [165]	Zibotentan vs placebo for patients with nonmetastatic CRPC, primary end point: progression-free survival and overall survival [208] Docetaxel + zibotentan vs docetaxel for patients with metastatic CRPC (recruitment finished); primary end point: overall survival [209]	No approval for PC treatment

For LOE, see Table 2.

ADT: Androgen deprivation therapy; BAP: Bone alkaline phosphatase; CL: Clodronate; CRPC: Castration-resistant prostate cancer; LOE: Level of evidence; NCT: National clinical trial; PA: Pamidronate; PC: Prostate cancer; PSA: Prostate-specific antigen; SRE: Skeletal-related event; ZA: Zoledronic acid.

Another bisphosphonate, pamidronate, with an *in vitro* potency (evaluated in experimental animals and, therefore, cannot be considered as equal to its possible clinical efficacy) of approximately 1:100 compared with zoledronic acid, was evaluated in a combined analysis of two Phase III trials (n = 378) for its ability to reduce bone pain and SREs in patients with metastatic prostate cancer and disease progression after first-line ADT [141]. Despite a 50% reduction of bone resorption markers in the pamidronate treatment arm, the drug failed to demonstrate a significant benefit compared with placebo with regard to the reduction of SREs and bone pain. It was assumed that lack of efficacy was due to an inadequate osteoclast inhibition by pamidronate, as compared with zoledronate with reduced urinary NTx levels by 70–80%, pamidronate was able to reduce NTx by only 50%. However, it should be noted that bone turnover markers are only surrogate parameters and that their levels do not equate with incidence of fractures and other SREs.

In a Phase III trial with 209 patients, intravenous clodronate, another bisphosphonate, failed to improve symptomatic disease PFS and OS, as well as overall quality of life of patients with CRPC [142]. In contrast to CRPC, there is only one randomized controlled trial, which investigated the role of bisphosphonates in patients with hormone-sensitive metastatic prostate cancer. In this Phase III study (n = 311), patients with hormone-sensitive prostate cancer undergoing ADT therapy either received oral clodronate or placebo. After 59 months, the clodronate group showed a nonsignificant improvement of symptomatic bone PFS (primary end point) and OS (secondary end point) [143]. Subgroup analysis suggested that the drug might be more effective the sooner after diagnosis of bone metastases treatment is started. In 2009, the 8-year OS data were published after 258 of the 311 enrolled patients had died [144]. The clodronate group demonstrated a significantly improved overall survival compared with placebo (22 vs 14%, p = 0.032). As zoledronic acid has been shown to be superior in the treatment of metastatic CRPC compared with clodronate, its efficacy in the treatment of hormone responsive PC is currently evaluated in a large Phase III trial with 680 patients enrolled [202].

Another important issue, which is evaluated in several clinical trials, is whether bisphosphonates are able to prevent the development of metastatic bone disease. Currently, the results of two randomized Phase III trials are available. In the MRC PR04 trial, patients with locally advanced stage T2–T4 prostate cancer (n = 508) without detectable bone metastases, who received external beam radiation therapy, a combination of hormonal and radiation therapy or primary hormonal therapy were either treated with placebo or oral clodronate [145]. The primary end point was the time to development of symptomatic bone metastases or prostate cancer death. With a median of almost 10 years of follow-up, clodronate demonstrated no benefit compared with placebo neither in the primary end point nor in the OS [144]. The Zometa 704 trial evaluated whether intravenous zoledronic acid is able to prolong the time to first bone metastasis in patients with nonmetastatic CRPC. For this study, a bone scan was performed every 4 months in patients, who either received zoledronate 4 mg every 4 weeks or placebo. Owing to a low event rate, the study was terminated 3 years after its onset in September 2002. At this point of time no significant difference in the time to first bone metastasis was observed. Since the role of zoledronic acid for the prevention of bone metastases is still unclear after Zometa 704 trial, the ongoing Zometa European Study (ZEUS) has been initiated. In this trial, 1443 patients without bone metastases and distinct risk factors, such as pN1 or PSA ≥20 ng/ml were randomized to standard prostate cancer therapy with or without zoledronic acid 4 mg i.v. every 3 months. Primary end point is the proportion of patients, who develop at least one bone metastasis after 48 months of therapy [203]. The ongoing Stampede Trial compares safety, PFS and OS of androgen suppression alone versus androgen suppression in varying combinations with zoledronate, docetaxel, prednisolone and celecoxib in patients with locally advanced or metastatic prostate cancer [204]. The final results of these studies are eagerly awaited. In contrast to other malignancies, such as myeloma and breast cancer, the application of bisphosphonates does not result in a significant reduction of pain in patients with prostate cancer according to a Cochrane review [146].

Denosumab

As osteoclastogenesis, an important process for the development of bone metastases, is driven by secretion of RANKL and other factors, RANKL inhibitors are of major interest in the treatment of metastatic bone disease. In preclinical studies, inhibition of RANKL by osteoprotegerin resulted in reduced growth of existing tumor lesions and prevented the development of new metastases [147–149]. In patients with metastatic bone disease (from PC, breast cancer or other neoplasms) and increased bone turnover despite i.v. bisphosphonate therapy, application of denosumab demonstrated a better ability to normalize bone turnover markers than continuation of bisphophonates did [150]. However, the rate of SREs, which formed the main clinical end point in this Phase III trial, was similar in both treatment arms. A significant reduction of bone turnover markers by the application of denosumab could also be observed in patients with metastatic breast cancer [151]. Ongoing Phase III studies are further evaluating, if denosumab is able to reduce the rate of SREs in patients with metastatic

prostate cancer. At the ASCO meeting 2010, the interim results of a Phase III study comparing denosumab to standard-of-care zoledronic acid for the prevention of SREs were presented. In patients with metastatic CRPC, denosumab significantly delayed the time to first on-study SRE compared with zoledronate (median time to first on study SRE 17.1 vs 20.7 months for zoledronate and denosumab; risk reduction 18%; p = 0.008). In this study, denosumab was also superior in reducing bone turnover markers compared with zoledronate. OS, time to cancer progression and adverse event rate were similar in the bisphosphonate and the denosumab arm [152]. The final results of this study are eagerly awaited. Similar effects were observed in patients with breast cancer. In a Phase III study, including 2000 patients with metastatic breast cancer, subcutaneously applied denosumab significantly delayed time to first SRE versus zoledronic acid [153]. For zoledronate, median time to first SRE was 26.4 months. Median time to first SRE for denosumab was not reached after 34 months. Remarkably, ONJ showed the same incidence (1.4 vs 2%, p = 0.39). Before, ONJ was assumed to be a class-specific side effect of nitrogen-containing bisphosphonates by many experts. As a result of these studies, denosumab has been currently approved by the FDA for the prevention of SREs in patients with solid tumors (including breast and prostate cancer). Other ongoing Phase III studies are evaluating the ability of denosumab to prevent bone metastases in patients with CRPC without bone metastases [205]. Until today, there is no data available, if denosumab has an effect on cancer-specific and overall survival in patients with metastatic prostate cancer.

Src–tyrosine kinase inhibition

Src, a nonreceptor tyrosine kinase, has a key function in the regulation of bone metabolism. High levels of Src are related with increased osteoclast activity [154]. Src also has a negative effect on osteoblast formation, and inhibition in mice leads to enhanced activity of osteoblasts [155]. Src has a tumor-promoting effect and increased Src activity can be observed in prostate cancer, particularly CRPC [156,157]. Inhibition in preclinical trials results in decreased *in vitro* and *in vivo* tumor growth [158]. In bone metastases, Src shows increased activity [157,159]. Inhibition of Src by antibodies, such as dasatinib or saracatinib, significantly reduced growth of bone metastases in animal prostate cancer models [160]. Owing to its positive effects on tumor growth and bone metabolism, Src kinase inhibitors are currently being investigated in clinical studies for their suitability for the treatment of prostate cancer. In a Phase II study, the application of dasatinib to patients with CRPC (n = 47) led to a reduction of progression (defined as tumor progression by RECIST or by at least one definite new lesion on bone scan) in 20 of 47 patients. Bone turnover markers were decreased in the majority of patients and even normalized in 53% of the patients, who had elevated urinary Ntx at the baseline of the study [108]. However, this study with a relatively low number of patients included was not placebo controlled, and other important end points, such as PSA decline ≥ 50% were only observed in a relatively low proportion of patients (three out of 47). A possible additive effect of dasatinib and docetaxel in patients with CRPC is tested in a randomized Phase III trial [206]. There is still lack of evidence whether decreased bone resorption achieved by dasatinib and a possible antiproliferative effect influence the clinical course of patients with prostate cancer. More clinical studies are needed to evaluate its potential for the treatment of metastatic bone disease. Src-inhibition still has to be considered as experimental therapy with low level of evidence.

Endothelin-A receptor antagonists

Other proteins, which are currently under investigation as specific targets for the treatment of bone metastases, are ET-1 and its receptors ET-A and ET-B. ET-1 is produced by a wide array of cells, including endothelial, mammary, endometrial and prostatic epithelial cells. ET-1 binds two receptors with different functions, the ET-A and ET-B receptor. Activation of the ET-A receptor promotes proliferation and survival, both in tumor cells and osteoblasts, and thereby promotes formation of osteoblastic bone metastases [161–163]. Activation of the ET-B receptor leads to cell death and apoptosis. After showing promising results in preclinical studies, atrasentan was the first ET-A receptor antagonist to be evaluated for effectiveness in CRPC. In a randomized, placebo-controlled Phase II study (n = 288), administration of atrasentan to patients with asymptomatic metastatic CRPC led to significantly prolonged time to progression in evaluable patients. Median time to PSA progression was twice as long as the placebo group (155 vs 71 days, p = 0.002). However, median time to progression in intent-to-treat patients was not prolonged significantly [164]. In a Phase III study (n = 809) the increase from baseline to final BAP and PSA levels was significantly lower in patients treated with atrasentan without meeting the relevant primary end point of prolonged time to progression (determined according to radiographic and clinical measures) [165]. Similar effects were seen in a Phase III trial of atrasentan for patients with nonmetastatic CRPC (n = 941). PSA doubling time could be lengthened and the increase of BAP slowed down without having a significant effect on time to progression [166]. Zibotentan is another ET-A receptor antagonist that shows no antagonistic activity at the proapoptotic ET-B receptor in contrast to

atrasentan [167]. The use of zibotentan in patients with CRPC and bone metastases was shown to lengthen OS (24.5 for the zibotentan 10 mg group vs 17.3 with placebo; p = 0.008) in a Phase II trial (n = 312). Zibotentan again did not show a significant effect on time to progression as primary end point [168]. Owing to these results, the zibotentan ENTHUSE Phase III trial program was initiated. This program consists of several clinical trials and evaluates the effect of zibotentan alone and in combination with docetaxel in patients with nonmetastatic and metastatic prostate cancer [207–209]. In September 2010, the sponsor announced that zibotentan alone (added to standard of care treatment) does not have a significant effect on OS of patients with metastatic CRPC. The final results of the complete study program will have a significant impact on the understanding of therapeutic effects of endothelin receptor antagonists and will enable the estimation of future perspectives on the use of these drugs in prostate cancer.

Radiopharmaceuticals

Besides external beam radiation therapy, bone-seeking radiopharmaceuticals, such as strontium-89 and samarium-153 have proven to significantly reduce bone pain in patients with metastatic bone disease [169–172]. In patients with widespread skeletal metastases, extended-field radiation may be useful, but is accompanied by serious side effects. In these cases, radiopharmaceuticals are a promising tool for palliation of pain, which are particularly effective in patients with osteoblastic bone metastases [173]. Strontium-89 and samarium-159 are incorporated as β-emitters into sclerotic bone metastases and their short-range radiation kills prostate cancer cells in bone. In general, these agents are well tolerated. Similarly to the extended field external beam radiation therapy, they can cause bone marrow suppression (external beam radiation with normal size field usually does not cause bone marrow suppression) [174] resulting in thrombocytopenia, which led to the widespread opinion that these agents should not be used in patients who are candidates for second-line chemotherapy. However, in a recently published Phase I study, repeated administration of samarium-153 with docetaxel in metastatic CRPC demonstrated manageable hematologic toxicity [175]. Consolidation therapy with samarium-153 after docetaxel chemotherapy could not reach the primary end point of prolonged PFS, but resulted in significantly improved pain control [176]. Radiopharmaceuticals have demonstrated benefits beyond pain relief. In a randomized Phase II trial (n = 72), bone-targeted consolidation therapy with Sr-89 plus doxorubicin once weekly for 6 weeks given to patients with stable or responding advanced CRPC after induction chemotherapy improved overall survival [177]. However, a positive effect of radiopharmaceuticals on clinical end points of patients with prostate cancer has not been confirmed in a Phase III study yet. Therefore, radiopharmaceuticals still lack enough clinical evidence to become standard treatment in metastatic prostate cancer in the near future.

Conclusion

Bone metastases and antihormonal treatment-induced bone loss have a significant impact on the clinical course and quality of life of patients with prostate cancer. In both cases, increased risk of fractures and other SREs are particularly caused by dysregulation of osteoclast activity and decreased bone stability. The imbalance of several molecular pathways regulating bone resorption and bone formation has been identified as the main reason for metastatic bone disease and osteoporosis due to iatrogenic hypogonadism, with the RANKL pathway being one of the important targets. The diagnosis of bone metastases remains a complex process with PSA representing a main indicator for disease progression and several imaging techniques competing for the highest hit rate and best ability to measure treatment response. Serum and urine markers are under intense investigation and are a valuable tool for the diagnosis of bone disease and evaluation of treatment response, although there are still important limitations that reduce their routine use in clinical practice. Either for ADT-induced bone loss and metastatic bone disease, bisphosphonates are able to decelerate reduction of bone mass. However, no data exist on whether its use can reliably prevent the development of fractures in nonmetastatic prostate cancer. Clinical results indicate that the RANKL antibody denosumab provides a valuable alternative to bisphosphonates. Both zoledronic acid and denosumab can prevent patients with bone metastases from fractures and other SREs. The inhibition of other molecular targets playing a key role in the interaction of tumor cells and bone microenvironment, such as ET-A and Src, is being investigated in clinical trials after providing promising results in preclinical studies. However, current results of ET-A receptor antagonism for metastatic CRPC indicate no benefit in OS.

Future perspective

The diagnosis and treatment of prostate cancer-related bone disease will remain a complex field with an increasing number of diagnostic and therapeutic tools available. As ADT is a major tool for the treatment of prostate cancer, which is increasingly used in earlier stages, effective strategies for the reduction and prevention of ADT-induced bone loss will become more and

more important. One strategy for preventing complications caused by ADT is intermittent androgen blockade, which has been shown to prevent bone loss [175], as testosterone recovery in the interval can provide time to bone recovery. With denosumab and toremifene, two drugs are available on the market that are not only able to reduce bone turnover markers but also improve the clinical course of patients by preventing skeletal complications during androgen deprivation therapy. Since most drugs targeting bone metabolism have major side effects, it is possible that their dose could be adjusted according to bone turnover markers measured in the patients' serum or urine. Bone turnover markers will gain importance both in early diagnosis, follow-up and indication for the therapy of bone metastases. Several markers have shown their ability to reliably reflect the patient's bone status. A better understanding of the complex interaction between host and tumor cells will lead to the development of new drugs for the treatment and prevention of bone metastases. Whether bisphosphonates and RANKL inhibitors are able to prevent the development of bone metastases, is currently under investigation in clinical trials. The results of these studies are likely to have a major impact on the treatment of prostate cancer especially in patients with early stages of the disease.

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Executive summary

Pathophysiology of androgen deprivation therapy-induced bone loss & metastatic bone disease

- Both androgen deprivation therapy (ADT)-induced osteoporosis and bone metastases have a significant effect on morbidity and mortality in prostate cancer.
- Increased bone turnover due to activation of osteoclasts is essential for the development of ADT-induced bone loss and bone metastases.
- RANKL is an important player in the interaction between tumor cells and microenvironment of the bone.

Diagnosis of ADT-induced bone loss

- Patients undergoing ADT should be screened for bone loss.
- Bone mineral density measurement alone is not sufficient to estimate fracture risk.
- Fracture risk models deliver a valuable tool to estimate the need for therapy.

Diagnosis of metastatic bone disease

- Bone scintigraphy is still the measure of choice for the detection of bone metastases.
- MRI can visualize bone metastases earlier and has a better sensitivity and specificity than bone scintigraphy.
- CT is the best technique to evaluate compromise of mechanical stability.
- Hybrid techniques combine functional and structural data but incur high cost.
- Serum and urine markers deliver a valuable tool for the detection of bone metastases.
- Marker levels correlate with therapy response.
- Bone turnover markers can be used for therapy decision.
- Interindividual variation and the variability of markers due to analytic and biologic factors reduce the routine use of bone turnover markers in clinical practice.

Strategies for the treatment of ADT-induced bone loss

- General measures to reduce fracture risk during ADT include cessation of smoking and alcohol consumption, exercise training and dietary intake of vitamin D and calcium.
- Bisphosphonates, denosumab and selective estrogen receptor modulators can reduce ADT-induced bone loss.
- Denosumab and toremifene significantly decrease incidence of skeletal-related events during ADT.

Bone-relevant strategies for the treatment of metastatic bone disease

- Bisphosphonates have shown efficacy in the reduction of skeletal-related events in patients with metastatic hormone-resistant prostate cancer and might improve overall survival in patients with hormone-sensitive metastatic prostate cancer.
- Denosumab delays time to first skeletal-related event in patients with metastatic castration-resistant prostate cancer.
- Ongoing studies evaluate, whether bisphosphonates and denosumab can prevent bone metastases in patients with nonmetastatic prostate cancer.
- Src inhibitors and Endothelin-A receptor antagonists result in clear biologic responses and are currently being investigated in clinical studies. Current results from a Phase III trial indicate, that in patients with metastatic prostate cancer, the endothelin-A-receptor antagonist zibotentan alone does not improve overall survival.
- Radiopharmaceuticals can palliate pain in patients with metastatic bone disease.

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