Review

Urologia Internationalis

Urol Int 2014;92:377–386
DOI: 10.1159/000358258

Published online: April 30, 2014

Richard Cathomas
Zoltan Bajory
Mounira Bouzid
Ahmed El Ghoneimy
Silke Gillessen
Frederico Goncalves
Gabriel Kacso
Gero Kramer
Piotr Milecki
Dalibor Pacik
Wahid Tantawy
Krzystof Lesniewski-Kmak

Division of Oncology and Hematology,
Department of Internal Medicine,
Cantonal Hospital Graubünden, Chur,
Switzerland

Management of Bone Metastases in Patients with Castration-Resistant Prostate Cancer

Key Words
Prostate cancer · Bone metastases · Skeletal-related events · Bone-targeted therapy · Radiotherapy · Surgery

Abstract
Bone metastases are a very common problem in prostate cancer. They are associated with considerable morbidity, adversely affect quality of life and frequently lead to advanced bone events (so-called skeletal-related events, SREs); SREs include fractures, spinal cord compression and the requirement for bone surgery or bone radiation. The aim of this paper was to evaluate currently available treatment options in the prevention and management of SREs and bone metastases in men with castration-resistant prostate cancer and to outline the importance of interdisciplinary management strategies. It also discusses the diagnostic workup of osseous metastases and practical considerations for the utilization of bone-targeted therapies in accordance with current guidelines to provide a consensus for special and/or difficult clinical situations.

Introduction

In men over the age of 50 years, prostate cancer (PCa) is the most commonly diagnosed cancer and the second leading cause of death by cancer [1]. PCa is one of the carcinomas with the highest rate of bone metastases. The standard first-line treatment of metastatic PCa is androgen deprivation therapy (ADT). ADT induces bone loss and can lead to osteoporosis [2, 3]. Treatment with ADT requires control of bone density and treatment accordingly. Maintaining bone health is therefore a very important issue for patients with advanced PCa early and late in their disease. Bone metastases can lead to skeletal-related events (SREs) or hypercalcemia. SREs include the need for analgetic radiotherapy to the bone, pathological fractures requiring radiotherapy or surgery and spinal cord compression. SREs are associated with an increased risk of death as well as increased health care costs and affect all aspects of quality of life, including physical, functional and emotional aspects [4].

KARGER

E-Mail karger@karger.com
www.karger.com/uin

0042–1138/14/0924–0377$39.50/0

Dr. Richard Cathomas
Abteilung Onkologie und Hämatologie, Departement Innere Medizin
Kantonsspital Graubünden
Loëstrasse 170, CH–7000 Chur (Switzerland)
E-Mail richard.cathomas@ksgr.ch

Treatment of bone metastases or prevention of SREs necessitates interventions and cooperation from different medical disciplines, including radiologists, orthopedic surgeons, neurosurgeons, radiation oncologists, medical oncologists, urologists, pain medicine specialists, dentists, physical medicine rehabilitation physicians and palliative care specialists. This review focuses on the management of bone metastases in patients with metastatic castration-resistant PCa (CRPC).

Preservation of Bone Health in PCa Patients Treated with ADT

Medically induced hypogonadism leads to bone loss and increased risk of fractures. All patients on long-term ADT (luteinizing hormone-releasing hormone analogs or after orchiectomy) should therefore be screened for bone mineral density and vitamin D levels should be measured. Daily supplementation of calcium and vitamin D is strongly suggested. Patients should be encouraged to eliminate risk factors for osteoporosis such as smoking and alcohol abuse and to exercise regularly for prevention of bone loss. A phase III trial demonstrated that the use of denosumab (60 mg every 6 months) significantly increased bone mineral density and reduced the risk of fractures in men under ADT [5]. Similar effects have been shown for the bisphosphonates zoledronate, pamidronate and alendronate, albeit in smaller trials.

Bone Metastases in Patients with Metastatic CRPC

In approximately 80% of PCa patients bone metastases represent the initial and main metastatic site and are an important prognostic factor [6, 7]. About half of PCa patients with untreated bone metastases will experience at least one SRE over the period of 2 years [8].

The knowledge of the mechanisms underlying the development of bone metastases and the correlation between bone and cancer cells is of special importance with regard to the different therapeutic options for the management and prevention of SREs. Bone metastases in PCa are frequently osteoblastic, however an osteolytic element has also been confirmed in various reports [9–13], and the majority of lesions tend to be heterogeneous [14].

Bone is a dynamic tissue remodeling itself permanently through the balanced activity of osteoblasts, cells that form new bone, and osteoclasts, which mediate bone resorption [15, 16]. Osteoblasts also express receptor activator of nuclear factor kappa-B ligand (RANKL), which binds to receptor activator of nuclear factor kappa-B (RANK) receptors on osteoclasts and their precursor cells. This binding of RANKL to RANK promotes the differentiation, activation and survival of osteoclasts. In healthy bone the regulation of RANK activity balances bone formation and bone resorption [15]. Tumor cells that have invaded bone secrete factors that increase RANKL expression by osteoblasts. The increased expression of RANKL results in excessive osteoclast activity, thus driving increased bone resorption, releasing growth factors from the bone matrix that may perpetuate tumor activity and drive the vicious cycle of bone destruction, potentially leading to SREs [16, 17].

In clinical trials of bone-modifying agents for the treatment of bone metastases, the incidence of SREs was used as a composite primary endpoint (e.g. time to first or subsequent SRE, incidence of SREs) [18], and they are recognized by the US Food and Drug Administration as a suitable endpoint to assess the efficacy of agents for the treatment of bone metastases in patients with cancer [19].

In patients with PCa, the levels of urinary cross-linked N-telopeptide of type I collagen (uNTx), a marker of bone resorption [20], and bone-specific alkaline phosphatase (BSAP), a marker of increased osteoblast activity and bone formation [21], are elevated, indicating a high bone turnover [22]. High concentrations of uNTx have been shown to be correlated with an increased risk of SREs and death in patients with bone metastases and PCa. Measurements of serum levels of BSAP, aminoterminal propeptide of procollagen type I (P1NP) and beta-isomer of carboxyterminal telopeptide of collagen I (β-CTX) were performed in a small prospective study in patients with PCa and bone metastases undergoing treatment with zoledronic acid [23]. β-CTX and P1NP were found to be predictors of mortality risk, while BSAP and P1NP predicted SREs.

Imaging of Bone Metastases

Many bone metastases are diagnosed incidentally and cause no or few symptoms. In symptomatic patients, pain is the most frequent symptom in about 75% of patients [24].

In the management of patients with PCa it is important to identify those patients who have progressed to an advanced stage of the disease and to assess the presence of metastatic bone lesions. For the detection of osseous lesions conventional radiography, computed tomography (CT), nuclear imaging and magnetic resonance im-

Table 1. Diagnosis of bone metastases in PCa

Standard imaging
Bone scan
CT scan
Special situations
MRI: especially before surgery, spinal cord compression

aging (MRI) are the four principal modalities used in the clinic [25, 26] (table 1). Most international guidelines still consider technetium-99 (^{99m}Tc) bone scintigraphy and plain X-ray radiography as the mainstay of imaging methods to detect and follow bone metastases [27, 28].

A plain X-ray radiograph is often an initial diagnostic test for evaluation of painful sites, but it is relatively insensitive in the detection of early or small metastatic lesions and does not detect osteolytic changes until a bone mineral loss of 50% has occurred [29].

^{99m}Tc is a nonspecific marker of osteoblastic activity and therefore used in nuclear imaging. It has relatively low costs and often represents the initial imaging technique for detection of bone metastases [30]. Radionuclide bone scans have a slightly lower sensitivity for purely osteolytic lesions, but they are highly sensitive to osteoblastic and mixed osteolytic-osteoblastic lesions such as from PCa [31].

However, due to the well-known lack of specificity of ^{99m}Tc bone scans, anatomic imaging such as CT or MRI is sometimes required for further evaluation [29]. Both CT and MRI can further assess suspicious findings on bone scans. MRI is especially valuable in detecting spinal metastases and in determining disease extension around the spinal cord as well as in aiding surgical and radiation therapy planning [32]. MRI has also shown some promise as a tool for evaluation of treatment response [25]. The role of MRI in identifying bone metastases is limited because it is more expensive and not as readily available as CT in several countries. Further development will focus on whole-body MRI [33]. The use of positron emission tomography in patients with PCa is under intense investigation. So far, the routine use of positron emission tomography for the diagnosis of bone metastases cannot be recommended.

Standard of Care for Patients with Metastatic CRPC and Bone Metastases

Several systemic treatment options have recently demonstrated excellent results with improvement of overall survival and disease control. They include the cytotoxic agents docetaxel and cabazitaxel, the antihormonal treatments abiraterone and enzalutamide as well as the radionuclide radium-223. In addition, the current medical treatment options for the prevention of SREs in CRPC patients with osseous metastases are bone-modifying therapies including bisphosphonates and the RANKL antibody denosumab [34]. The primary goal of treatment is to reduce the morbidity due to SREs so that quality of life and functional independence can be preserved or improved. Clinical guidelines recommend that treatment with bone-targeted drugs should be started in patients with CRPC who have evidence of bone metastases [28, 35, 36], although the point of time to initiate the treatment is at the physician's discretion [37, 38]. In case of symptomatic bone metastases local radiotherapy, surgery or treatment with radionuclides can be beneficial. Most of the mentioned systemic and local treatments have demonstrated a significant impact on pain control and hence on quality of life. Additionally, correct pain assessment and adequate analgetic treatment according to the principles of pain management as published in guidelines has to be applied at any time [39].

Radiotherapy

The main indications for radiotherapy are localized constant or breakthrough pain not sufficiently controlled by analgesia, pathological fractures following surgical fixation (postoperative radiotherapy), spinal cord compression after surgery or if surgery is not possible, prevention of morbidity from uncomplicated bone metastases and inoperable pathological fractures. In the treatment of bone metastases two kinds of radiotherapy can be distinguished, external beam radiation and systemic radiotherapy with radioisotopes.

Different fractionation schedules can provide significant palliation of symptoms and prevent morbidity of bone metastases. With external beam radiation, pain relief is obtained in 50–80% of patients, with complete pain relief in up to 30% of patients. The onset of pain relief varies from a few days to 4 weeks, re-irradiation should therefore not be considered sooner than 4 weeks after the initial radiotherapy. In clinical studies, the median duration of pain relief obtained was 3–6 months [40–42].

Historically, the treatment of multiple bone metastases comprises half-body irradiation [43, 44] and systemic β-emitter radionuclides such as strontium-89 [45] and samarium-153. The side effects of radiopharmaceuticals and half-body irradiation include bone marrow suppression, which may be worse in heavily pretreated patients [32] and may compromise future chemotherapy treat-

ment. Additionally, no survival benefit has been demonstrated with these techniques, and pain flare has been described. Contraindications for treatment with radionuclides are risk of fracture, nerve or spinal cord compression and urinary incontinence. While half-body irradiation, strontium and samarium have not been used extensively, the results of a new radionuclide, radium-223, will likely increase the use of radionuclides in the near future: A randomized placebo-controlled phase III study (the ALSYMPCA trial) [46] of patients with CRPC and two or more bone metastases evaluated radium-223, an α-particle emitter with high affinity for the bone matrix. 921 patients were randomized to receive radium-223 (50 kBq/kg) in 6 injections at 4-week intervals or placebo. The radionuclide demonstrated a significantly prolonged overall survival of 14.0 months (versus 11.2 months in the placebo group, p = 0.00185) with no differences in grade 3 or 4 hematologic adverse events. Moreover, a remarkable advantage in favor of radium-223 compared to placebo was found regarding SREs: time to the first SRE was significantly delayed (median 13.6 vs. 8.4 months, p = 0.00046).

Surgery

The operative management of skeletal metastases is determined by factors such as expected duration of survival, potential of rehabilitation, overall medical condition and type of intervention required. The role of orthopedic surgery can be to confirm the diagnosis, to treat spinal cord compression and to prevent existing or impending pathological fractures. Surgery may be required to provide stabilization, to restore function and ambulation, even in patients with very short life expectancies, and to relieve pain that does not respond to any nonoperative methods [47–49]. Treatment of impending fractures is associated with a shorter hospital stay, a greater likelihood of discharge to home versus extended care, and a greater likelihood of support-free ambulation [50].

An adequate and detailed preoperative assessment should be conducted to evaluate the scope of local bone destruction and soft tissue involvement as well as overall medical and oncological status. Decisions should be taken in a multidisciplinary team.

Management of Spinal Cord Compression

In case of vertebral column instability, vertebral compression, neurological symptoms and/or acute paraplegia, immediate workup with MRI is mandatory. This specific category of patients with spinal cord compression due to metastatic bone and neurological symptoms is an oncological emergency and needs swift interdisciplinary cooperation between radiation oncologists, urologists, orthopedic surgeons, neurosurgeons and medical oncologists. Surgical decompression with tumor debulking followed by radiotherapy is the procedure of choice [51], taking into account that laminectomy additionally destabilizes the vertebral column [52, 53]. It is important to urgently perform MRI as short as possible after the onset of neurological symptoms, and treatment should be initiated within 24–48 h after onset of the symptoms if possible. Surgery provides a greater probability of return to ambulatory condition than radiation alone; local tumor control is generally accomplished by postoperative radiation therapy, with or without prior operative removal of the tumor [54]. A randomized study evaluated the efficacy of surgical treatment and radiation therapy compared with that of radiation therapy alone in patients with spinal metastasis and spinal cord compression [52]. The primary endpoint in this study was the capability to walk. The results demonstrated that significantly more patients were able to walk after treatment in the surgery group than in the radiation therapy group (odds ratio 6.2, 95% confidence interval 2.0–19.8, p = 0.001). Thus, it can be concluded that decompressive surgery followed by postoperative radiation therapy can be superior to radiation therapy alone for selected patients with spinal metastases and spinal cord compression [54]. Only in selected cases may external beam radiation as monotherapy be chosen for treatment of spinal cord compression [51].

Techniques like radiosurgery and stereotactic body radiation therapy could be beneficial for selected patients, including those with recurrent spinal cord compression [55, 56] and vertebral metastases. Stereotactic body radiation therapy may be particularly helpful in the re-irradiation setting [32].

Bisphosphonates

The nitrogen-containing bisphosphonates or aminobisphosphonates (pamidronate, zoledronic acid, ibandronate) interfere with the mevalonate metabolism by blocking specific enzymes of cholesterol biosynthesis in osteoclasts, which promotes subsequent changes in the cytoskeletal function and osteoclast apoptosis.

Zoledronic acid is the most extensively evaluated bisphosphonate for PCa and has been shown to prevent bone loss in patients with PCa undergoing ADT [57] and to reduce the incidence of SREs in metastatic PCa [8, 58]. The bisphosphonates pamidronate and clodronate failed to show a significant impact on progression of bone metastases in randomized trials [59, 60]. Of note, however, an update of the clodronate study demonstrated an im-

Table 2. Adverse events in patients receiving zoledronic acid or denosumab

Adverse events	Zoledronic acid 4 mg i.v.	Denosumab 120 mg s.c.
Renal toxicity	+++	+
Nausea	+	+
Fatigue	+	+
Bone pain	+	+
Asthenia	+	+
Arthralgia	+	+
Acute-phase reactions	+++	+
Hypocalcemia	+	++
Cumulative ONJ (year 2)	+	++
CTCAE grade 3 or 4 adverse events	++(+)	+++

CTCAE = Common Terminology Criteria for Adverse Events (version 3.0) [63].

provement of overall survival in nonmetastatic PCa patients, but not in metastatic patients [61]. Due to the small patient numbers and the unplanned nature of this subgroup analysis, this study is not widely accepted and has not had any impact on clinical practice or guidelines. A prospective, randomized, placebo-controlled phase III study of zoledronic acid assessed the treatment with zoledronic acid versus placebo in 643 patients with metastatic CRPC [58]. The primary endpoint was the proportion of patients with ≥1 SRE (defined as radiation to bone, pathological fracture, spinal cord compression, surgery to bone or change in antineoplastic therapy). Zoledronic acid 4 mg reduced the proportion of patients with ≥1 SRE versus placebo: at 15 months the incidence of at least one SRE was seen in significantly more patients who received placebo than in the 4 mg zoledronic acid group (44.2 vs. 33.2%, respectively, p = 0.021). Despite the differences in SREs, there were no differences in measures of disease progression or overall survival. After 24-month follow-up, the time to first SRE for the 4 mg zoledronic acid group was prolonged (321 vs. 488 days, p = 0.0009); furthermore the continuing risk of an SRE was reduced by 36% compared with placebo (p = 0.002), and fewer patients in the 4 mg zoledronic acid group than in the placebo group had at least one SRE (38 vs. 49%, p = 0.028) [8].

Denosumab

Denosumab is a fully human monoclonal IgG2 antibody that binds human RANKL with high affinity and specificity. Subsequently denosumab prevents RANKL from activating its receptor RANK on the surface of osteoclasts and their precursor cells, which results in inhibition of osteoclast-mediated bone resorption in bone metastases from solid tumors and multiple myeloma [62]. Denosumab is administered as a subcutaneous injection and is not excreted through the kidney.

In a randomized, double-blind phase III study, patient with metastatic CRPC were randomized between denosumab and zoledronic acid [63]. 951 patients were assigned to receive zoledronic acid (4 mg i.v. every 4 weeks) and 950 received denosumab (120 mg s.c. every 4 weeks). The primary endpoint was the time to first SRE (including pathological fracture, radiation therapy, surgery to bone or spinal cord compression). Adverse events in patients receiving zoledronic acid or denosumab are listed in table 2.

Denosumab delayed the time to first SRE by 18% (relative reduction) compared to zoledronic acid, with a between-group difference of 3.6 months (denosumab 20.7 months, zoledronic acid 17.1 months; hazard ratio 0.82, 95% confidence interval 0.71–0.95, p = 0.0002 for noninferiority and 0.008 for superiority). Pain severity outcomes from this study showed that a numerically lower proportion of patients treated with denosumab experienced pain severity progression from baseline compared with zoledronic acid at each assessment time point [64].

Denosumab has also been tested in CRPC patients with no evidence of bone metastases. This large double-blind, randomized, placebo-controlled, phase III trial demonstrated that treatment with denosumab could delay bone metastasis in men with CRPC: 1,432 patients with nonmetastatic CRPC at high risk of bone metastasis (defined as prostate-specific antigen (PSA) ≥8.0 μg/l or PSA doubling time ≤10.0 months, or both) were randomly assigned to receive denosumab 120 mg or placebo every 4 weeks. The primary endpoint was bone metastasis-free survival. In summary, denosumab was related to improved bone metastasis-free survival by a median of 4.2 months compared with placebo (median 29.5 vs. 25.2 months; hazard ratio 0.85, 95% confidence interval 0.73–0.98, p = 0.028), representing a relative risk reduction of 15% [65]. However, no impact on overall survival was noted.

Safety

Current antiresorptive therapies are generally well tolerated. Nevertheless, it is important to recognize adverse events and to understand the common class effects and class-specific differences in order to increase the safety for patients.

Acute-Phase Reactions. Well-known treatment-associated side effects, especially with intravenous bisphosphonates, include a rise in body temperature accompanied by flu-like symptoms (chills, flushing, bone pain and/or arthralgias, myalgias) that resemble a typical acute-phase response [66–69]. These clinical features occur mainly after the initial infusions of aminobisphosphonates in up to one third of patients [69, 70]. They are generally transient, mild, reversible and decrease in severity after the first or second infusion [71, 72]. In patients with bone metastases from PCa, acute-phase reactions occurred significantly more often with zoledronic acid than with denosumab (18 vs. 8%) [63]. Similar results were found in the phase III trials for breast cancer and other solid tumors [73, 74].

Hypocalcemia. Another reported adverse event during the use of antiresorptive therapies is hypocalcemia which, untreated, may result in cataract formation, prolonged QT interval, seizures, hypotension, congestive heart failure or dementia [75]. To reduce the risk of hypocalcemia, calcium levels should be monitored and patients receiving bisphosphonates or denosumab should receive adequate calcium and vitamin D supplementation. In clinical trials, hypocalcemia was more frequent in patients treated with denosumab compared with zoledronic acid in the advanced cancer setting [63, 73, 74]. Patients with a creatinine clearance <30 ml/min or receiving dialysis are at higher risk for developing hypocalcemia [76].

Renal Side Effects. Each bisphosphonate has known dose- and infusion rate-dependent effects on renal function [77], thus renal monitoring before each bisphosphonate therapy with following dose adjustments is recommended for some intravenous bisphosphonates. The dose for zoledronic acid must be adjusted for impaired renal function with a glomerular filtration rate <60 ml/min and zoledronic acid is contraindicated if the glomerular filtration rate is <30 ml/min. Unless creatinine clearance is >30 ml/min, denosumab has no effect on renal function and therefore renal monitoring or dose adjustments are not required [78–80].

Osteonecrosis of the Jaw (ONJ). ONJ lesions have been reported in patients with advanced cancers treated with oral and intravenous antiresorptive therapies [81–83]. The phase III trials with denosumab in patients with bone metastases from solid tumors or multiple myeloma prospectively assessing the incidence of ONJ showed a similar or numerically higher rate of ONJ with denosumab (2.2% for PCa, 1.1% for solid tumors/multiple myeloma, 2.0% for breast cancer; 52 cases in total) as compared with zoledronic acid (1.1% for PCa, 1.3% for solid tumors/multiple myeloma, 1.4% for breast cancer) [63, 73, 74]. Known risk factors for developing ONJ are invasive dental procedures and poor oral hygiene [84]. The risk for the development of an ONJ lesion may also be related to duration of therapy, timing of administration of antiresorptive therapy relative to dental surgery concomitant chemotherapy and other medications, and the underlying disease [85, 86]. According to current guidelines, oral hygiene, baseline dental evaluation for high-risk individuals and avoidance of invasive dental surgery during therapy are recommended to reduce the risk of ONJ [35]. It is therefore recommended to have a baseline dental evaluation before the start of therapy and work closely together with a dentist experienced in this field.

Ocular Complications. Rarely, ocular adverse events have been noticed in patients receiving intravenous bisphosphonates and denosumab, including eyelid edema, scleritis, episcleritis, conjunctivitis, orbital inflammation and cranial nerve palsy. They usually occur within 48 h after infusion and are transient and well treatable with steroids [87].

Conclusive Recommendations

In patients with CRPC and documented bone metastases, treatment and monitoring should integrate a multidisciplinary approach that if indicated involves systemic therapy, bone-targeted therapy as well as surgery and radiation therapy.

Bone-targeted drugs have been widely evaluated in randomized clinical trials in metastatic CRPC patients, and currently two bone-targeted therapies are approved for use in CRPC patients with bone metastases. Both zoledronic acid and the RANKL inhibitor denosumab have been shown to decrease the proportion of SREs and to delay the median time to the first event. According to clinical evidence, denosumab is superior to zoledronic acid in delaying the median time to the first on-study SRE [60]. None of the two substances demonstrated clear effects on overall survival or quality of life outcomes. Choosing whether to start therapy and which therapy to use should be based on the advantages and disadvantages of each therapy as well as the needs of each individual patient.

The use of denosumab in clinical routine has some advantages: there is no contraindication in patients with impaired renal function, the route of administration is more convenient and the incidence of acute-phase reactions is lower [88].

ONJ is reported with both agents; the risk of osteonecrotic lesions is increased in patients who have tooth extractions, poor dental hygiene or a dental appliance. Therefore oral hygiene and dental status (best during the hormone-sensitive phase, invasive procedures before start) have to be examined prior to start, and avoidance of invasive dental surgery during therapy is also recommended to reduce risk. The risk of ONJ is cumulative and increases with extended bone-targeted therapy. It is helpful to have an experienced dentist as part of the multidisciplinary team.

Factors surrounding the use of zoledronic acid and denosumab are differences in administration, cost-effectiveness considerations, sequence of agents and the use of agents with concomitant systemic therapy including chemotherapy, biologic therapy as well as side effects of disease and treatment. The decision to treat is often individualized, based on different patient categories, the patient's clinical presentation, life expectancy and quality of life. The treatment with bone-targeted drugs (in doses used for prevention of SREs) should for the time being only be initiated in patients with PCa if (1) the patient has castration-resistant disease and (2) bone metastases are present. In the authors' opinion the following further points should be fulfilled to consider the use of bone-targeted drugs: (3) the patient's life expectancy should be at least 6 months, (4) PSA doubling time should be <6 months, and (5) performance status should be 0–2 (or performance status 3 due to symptomatic bone metastases). Furthermore it is debatable whether patients with oligometastatic disease (1–3 bone metastases) derive the same benefit of the treatment. Response to tumor-specific treatment or the patient's Gleason score should not be used for the decision to start treatment. Bone-targeted therapy is never an emergency treatment. Prior to start, validation of serum calcium and renal function is mandatory.

The optimal duration of treatment for either zoledronic acid or denosumab as well as a potential sequential use of denosumab following bisphosphonate therapy remain uncertain and will be based on clinical judgment.

Switching from one bone-targeted therapy to another can be considered in case of drug intolerance (e.g. acute-phase reaction) or increased pain, although there are limited data and further trials are necessary.

Regarding antiresorptive therapies in metastatic hormone-sensitive patients there is lack of data, hence the use of denosumab or zoledronic acid in this setting cannot be recommended outside of clinical trials. It is important to note that denosumab and zoledronic acid have been shown to prevent and treat osteoporosis induced by ADT. For this indication, denosumab and zoledronic acid are used in different doses and schedules.

Due to missing information on differences in quality of life and lacking impact on overall survival, the cost-effectiveness of denosumab versus zoledronic acid is difficult to calculate. The identification of selected patients with higher benefit from treatment with denosumab in the future (bone turnover/predictive markers) could lead to improved cost-effectiveness calculations.

In summary, the treatment of bone metastases in CRPC patients and the choice of treatment requires a close cooperation between oncologists, radiologists, urologists, orthopedic surgeons, dentists and pain medicine specialists. Interdisciplinary management remains the mainstay for the management of these patients.

Acknowledgments

The authors thank Martin Langeder of Update Europe GesmbH, Vienna, Austria, for providing writing and editorial support.

References

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–2917.
2 Townsend MF, Sanders WH, Northway RO, Graham SD Jr: Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate carcinoma. Cancer 1997;79:545–550.
3 Collinson MP, Tyrell CJ, Hutton C: Osteoporosis occurring in two patients receiving LHRH analogs for carcinoma of the prostate. Calcif Tissue Int 1994;54:327–328.
4 Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, Schulman KA: The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Ann Oncol 2005;16:579–584.
5 Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, Heracek J, Szwedowski M, Ke C, Kupic A, Leder BZ, Goessl C; Denosumab HALT Prostate Cancer Study Group: Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009;361:745–755.
6 Rigaud J, Tiguert R, Le Normand L, Karam G, Glemain P, Buzelin JM, Bouchot O: Prognostic value of bone scan in patients with metastatic prostate cancer treated initially with androgen deprivation therapy. J Urol 2002;168:1423–1426.

7 Soloway MS, Hardeman SW, Hickey D, Raymond J, Todd B, Soloway S, Moinuddin M: Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer 1988;61:195–202.

8 Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Zheng M; Zoledronic Acid Prostate Cancer Study Group: Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004;96:879–882.

9 Halvorson KG, Sevcik MA, Ghilardi JR, Rosol TJ, Mantyh PW: Similarities and differences in tumor growth, skeletal remodeling and pain in an osteolytic and osteoblastic model of bone cancer. Clin J Pain 2006;22:587–600.

10 Charhon SA, Chapuy MC, Delvin EE, Valentin-Opran A, Edouard CM, Meunier PJ: Histomorphometric analysis of sclerotic bone metastases from prostatic carcinoma with special reference to osteomalacia. Cancer 1983;51:918–924.

11 Clarke NW, McClure J, George NJ: Morphometric evidence for bone resorption and replacement in prostate cancer. Br J Urol 1991; 68:74–80.

12 Clarke NW, McClure J, George NJ: Disodium pamidronate identifies differential osteoclastic bone resorption in metastatic prostate cancer. Br J Urol 1992;69:64–70.

13 Percival RC, Urwin GH, Harris S, Yates AJ, Williams JL, Beneton M, Kanis JA: Biochemical and histological evidence that carcinoma of the prostate is associated with increased bone resorption. Eur J Surg Oncol 1987;13:41–49.

14 Stenzl A: RANK ligand: a key role in cancer-induced bone destruction? Eur Urol Suppl 2009;8:823–828.

15 Boyle WJ, Simonet WS, Lacey DL: Osteoclast differentiation and activation. Nature 2003; 423:337–342.

16 Roodman GD: Mechanisms of bone metastasis. N Engl J Med 2004;350:1655–1664.

17 Mundy GR: Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer 2002;2:584–593.

18 Johnson JR, Williams G, Pazdur R: End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 2003;21:1404–1411.

19 US Food and Drug Administration, Center for Drug Evaluation and Research: Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf (accessed February 25, 2011).

20 Hanson DA, Weis MA, Bollen AM, Maslan SL, Singer FR, Eyre DR: A specific immunoassay for monitoring human bone resorption: quantitation of type I collagen cross-linked N-telopeptides in urine. J Bone Miner Res 1992;7:1251–1258.

21 Ureña P, Hruby M, Ferreira A, Ang KS, de Vernejoul MC: Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. J Am Soc Nephrol 1996;7:506–512.

22 Coleman RE, Major P, Lipton A, Brown JE, Lee KA, Smith M, Saad F, Zheng M, Hei YJ, Seaman J, Cook R: Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. J Clin Oncol 2005;23:4925–4935.

23 de la Piedra C, Alcaraz A, Bellmunt J, Meseguer C, Gómez-Caamano A, Ribal MJ, Vázquez F, Anido U, Samper P, Esteban E, Álvarez-Ossorio JL, Lara PC, San José LA, Contreras JA, del Alba AG, González-Gragera B, Tabernero AJ, González-Enguita C, Fernández JM, García-Escudero A, Gómez-Veiga F, Méndez MJ, Segarra J, Virizuela JA, Carles J, Lassa A, Calderero V, Constela M, Delgado D, Mañas A, Murias A, Reynes G, Rodriguez B, Rubio G, Sánchez E, Unda M, Solsona E, Martínez-Javaloyas JM, Comet-Batlle J, Quicios C, Martín-Fernández M, Mahillo-Fernández I, Morote J: Usefulness of bone turnover markers as predictors of mortality risk, disease progression and skeletal-related events appearance in patients with prostate cancer with bone metastases following treatment with zoledronic acid: TUGAMO study. Br J Cancer 2013;108: 2565–2572.

24 Ibrahim T, Farolfi A, Mercatali L, Ricci M, Amadori D: Metastatic bone disease in the era of bone-targeted therapy: clinical impact. Tumori 2013;99:1–9.

25 Rybak LD, Rosenthal DI: Radiological imaging for the diagnosis of bone metastases. Q J Nucl Med 2001;45:53–64.

26 Heidenreich A, Albers P, Classen J, Graefen M, Gschwend J, Kotzerke J, Krege S, Lehmann J, Rohde D, Schmidberger H, Uder M, Zeeb H; Association of Urologic Oncology of the German Cancer Society: Imaging studies in metastatic urogenital cancer patients undergoing systemic therapy: recommendations of a multidisciplinary consensus meeting of the Association of Urological Oncology of the German Cancer Society. Urol Int 2010;85:1–10.

27 National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology. Prostate Cancer, vol 1, 2011.

28 Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, Mason MD, Matveev V, Mottet N, van der Kwast TH, Wiegel T, Zattoni F: Guidelines on Prostate Cancer. European Association of Urology 2013, update March 2013. http://www.uroweb.org/gls/pdf/09_Prostate_Cancer_LR.pdf.

29 Rosenthal DI: Radiologic diagnosis of bone metastases. Cancer 1997;80(8 suppl):1595–1607.

30 Schaffer DL, Pendergrass HP: Comparison of enzyme, clinical, radiographic, and radionuclide methods of detecting bone metastases from carcinoma of the prostate. Radiology 1976;121:431–434.

31 Gralow JR, Biermann JS, Farooki A, Fornier MN, Gagel RF, Kumar RN, Shapiro CL, Shields A, Smith MR, Srinivas S, van Poznak CH: NCCN task force report: bone health in cancer care. J Natl Compr Canc Netw 2009; 7(suppl 3):S1–S32; quiz S33–S35.

32 Yu HH, Tsai YY, Hoffe SE: Overview of diagnosis and management of metastatic disease to bone. Cancer Control 2012;19:84–91.

33 Tombal B, Lecouvet F: Modern detection of prostate cancer's bone metastasis: is the bone scan era over? Adv Urol 2012;2012:893193.

34 Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A: Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010;28:5132–5139.

35 National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology 2011. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed November 26, 2012).

36 Saad F, Hotte SJ: Guidelines for the management of castrate-resistant prostate cancer. Can Urol Assoc J 2010;4:380–384.

37 Heidenreich A, Witjes WP, Bjerklund-Johansen TE, Patel A; EAU Research Foundation: Therapies used in prostate cancer patients by European urologists: data on indication with a focus on expectations, perceived barriers and guideline compliance related to the use of bisphosphonates. Urol Int 2012;89:30–38.

38 So A, Chin J, Fleshner N, Saad F: Management of skeletal-related events in patients with advanced prostate cancer and bone metastases: incorporating new agents into clinical practice. Can Urol Assoc J 2012;6:465–470.

39 Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F; ESMO Guidelines Working Group: Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23(suppl 7):vii139–vii154.

40 Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach M 3rd, Suh JH, Demas WF, Movsas B, Petersen IA, Konski AA, Cleeland CS, Janjan NA, DeSilvio M: Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 2005;97:798–804.

41 Foro Arnalot P, Fontanals AV, Galcerán JC, Lynd F, Latiesas XS, de Dios NR, Castillejo AR, Bassols ML, Galán JL, Conejo IM, López MA: Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiother Oncol 2008;89:150–155.

42 Sande TA, Ruenes R, Lund JA, Bruland OS, Hornslien K, Bremnes R, Kaasa S: Long-term follow-up of cancer patients receiving radiotherapy for bone metastases: results from a randomised multicentre trial. Radiother Oncol 2009;91:261–266.

43 Dearnaley DP, Bayly RJ, A'Hern RP, Gadd J, Zivanovic MM, Lewington VJ: Palliation of bone metastases in prostate cancer. Hemibody irradiation or strontium-89? Clin Oncol (R Coll Radiol) 1992;4:101–107.

44 Salazar OM, Sandhu T, da Motta NW, Escutia MA, Lanzós-Gonzales E, Mouelle-Sone A, Moscol A, Zaharia M, Zaman S: Fractionated half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomized phase III trial of the International Atomic Energy Agency (IAEA). Int J Radiat Oncol Biol Phys 2001;50:765–775.

45 Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H, Sathyanarayana JR, Yakemchuk VN, Thomas GM, Erlich LE, et al: Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. Int J Radiat Oncol Biol Phys 1993;25:805–813.

46 Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, Chodacki A, Wiechno P, Logue J, Seke M, Widmark A, Johannessen DC, Hoskin P, Bottomley D, James ND, Solberg A, Syndikus I, Kliment J, Wedel S, Boehmer S, Dall'Oglio M, Franzén L, Coleman R, Vogelzang NJ, O'Bryan-Tear CG, Staudacher K, Garcia-Vargas J, Shan M, Bruland ØS, Sartor O; ALSYMPCA Investigators: Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–223.

47 Bickels J, Kollender Y, Wittig JC, Meller I, Malawer MM: Function after resection of humeral metastases: analysis of 59 consecutive patients. Clin Orthop Relat Res 2005; 437:201–208.

48 Harrington KD: Impending pathologic fractures from metastatic malignancy: evaluation and management. Instr Course Lect 1986;35:357–381.

49 Kollender Y, Bickels J, Price WM, Kellar KL, Chen J, Merimsky O, Meller I, Malawer MM: Metastatic renal cell carcinoma of bone: indications and technique of surgical intervention. J Urol 2000;164:1505–1508.

50 Ward WG, Holsenbeck S, Dorey FJ, Spang J, Howe D: Metastatic disease of the femur: surgical treatment. Clin Orthop Relat Res 2003;415(suppl):S230–S244.

51 Rades D, Huttenlocher S, Dunst J, Bajrovic A, Karstens JH, Rudat V, Schild SE: Matched pair analysis comparing surgery followed by radiotherapy and radiotherapy alone for metastatic spinal cord compression. J Clin Oncol 2010;28:3597–3604.

52 Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M, Young B: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 2005;366:643–648.

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

54 Bickels J, Dadia S, Lidar Z: Surgical management of metastatic bone disease. J Bone Joint Surg Am 2009;91:1503–1516.

55 Sahgal A, Larson DA, Chang EL: Stereotactic body radiosurgery for spinal metastases: a critical review. Int J Radiat Oncol Biol Phys 2008;71:652–655.

56 Chang EL, Shiu AS, Mendel E, Mathews LA, Mahajan A, Allen PK, Weinberg JS, Brown BW, Wang XS, Woo SY, Cleeland C, Maor MH, Rhines LD: Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. J Neurosurg Spine 2007;7:151–160.

57 Coleman RE, Rathbone E, Brown JE: Management of cancer treatment-induced bone loss. Nat Rev Rheumatol 2013;9:365–374.

58 Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Chen B; Zoledronic Acid Prostate Cancer Study Group: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458–1468.

59 Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC, Thompson PM, Moffat LE, Naylor SL, Parmar MK; Mrc Pr05 Collaborators: A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). J Natl Cancer Inst 2003;95: 1300–1311.

60 Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO: Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. J Clin Oncol 2003;21: 4277–4284.

61 Dearnaley DP, Mason MD, Parmar MK, Sanders K, Sydes MR: Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. Lancet Oncol 2009;10:872–876.

62 Body JJ, Facon T, Coleman RE, Lipton A, Geurs F, Fan M, Holloway D, Peterson MC, Bekker PJ: A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res 2006;12:1221–1228.

63 Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C: Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011; 377:813–822.

64 Brown JE, Cleeland CS, Fallowfield LJ, Patrick DL, Fizazi K, Smith MR, Maroto JP, Michel MS, Feng A, Goessl C, Chung K: Pain outcomes in patients with bone metastases from castrate-resistant prostate cancer: results from a phase 3 trial of denosumab vs. zoledronic acid. Eur Urol 2011;10(2 suppl): 336.

65 Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, Miller K, Sieber P, Karsh L, Damião R, Tammela TL, Egerdie B, van Poppel H, Chin J, Morote J, Gómez-Veiga F, Borkowski T, Ye Z, Kupic A, Dansey R, Goessl C: Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 2012;379:39–46.

66 Bock O, Boerst H, Thomasius FE, Degner C, Stephan-Oelkers M, Valentine SM, Felsenberg D: Common musculoskeletal adverse effects of oral treatment with once weekly alendronate and risedronate in patients with osteoporosis and ways for their prevention. J Musculoskelet Neuronal Interact 2007; 7:144–148.

67 Maxwell C, Swift R, Goode M, Doane L, Rogers M: Advances in supportive care of patients with cancer and bone metastases: nursing implications of zoledronic acid. Clin J Oncol Nurs 2003;7:403–408.

68 Olson K, van Poznak C: Significance and impact of bisphosphonate-induced acute phase responses. J Oncol Pharm Pract 2007;13: 223–229.

69 Adami S, Bhalla AK, Dorizzi R, Montesanti F, Rosini S, Salvagno G, Lo Cascio V: The acute-phase response after bisphosphonate administration. Calcif Tissue Int 1987;41: 326–331.

70 Gallacher SJ, Ralston SH, Patel U, Boyle IT: Side-effects of pamidronate. Lancet 1989;2: 42–43.

71 Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, Apffelstaedt J, Hussein MA, Coleman RE, Reitsma DJ, Chen BL, Seaman JJ: Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003;98:1735–1744.

72 Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krzakowski M, Pawlicki M, De Souza P, Zheng M, Urbanowitz G, Reitsma D, Seaman J: Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind, placebo-controlled trial. Cancer 2004;100:2613–2621.

73 Stopeck A, Fallowfield L, Patrick D, Cleeland CS, De Boer RH, Steger GG, Qian Y, Jiang Q, Dansey RD, Chung K: Effects of denosumab versus zoledronic acid (ZA) on pain in patients (pts) with metastatic breast cancer: results from a phase III clinical trial (abstract). J Clin Oncol 2010;28(suppl 15):A1024.

74 Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, Scagliotti GV, Sleeboom H, Spencer A, Vadhan-Raj S, von Moos R, Willenbacher W, Woll PJ, Wang J, Jiang Q, Jun S, Dansey R, Yeh H: Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011;29:1125–1132.

75 Skugor M: Hypocalcemia. Cleveland, The Cleveland Clinic Foundation, 2004. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/hypocalcemia/.

76 European Medicines Agency: Assessment Report for XGEVA. European Medicines Agency, 2011. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002173/WC500110384.pdf.

77 Hadji P, Aapro M, Costa L, Gnant M: Antiresorptive treatment options and bone health in cancer patients – safety profiles and clinical considerations. Cancer Treat Rev 2012;38:815–824.

78 Fizazi K, Lipton A, Mariette X, Body JJ, Rahim Y, Gralow JR, Gao G, Wu L, Sohn W, Jun S: Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol 2009;27:1564–1571.

79 Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, Fan M, Jun S: Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol 2008;26:4875–4882.

80 Lipton A, Steger GG, Figueroa J, Alvarado C, Solal-Celigny P, Body JJ, de Boer R, Berardi R, Gascon P, Tonkin KS, Coleman R, Paterson AH, Peterson MC, Fan M, Kinsey A, Jun S: Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. J Clin Oncol 2007;25:4431–4437.

81 Estilo CL, van Poznak CH, Wiliams T, Bohle GC, Lwin PT, Zhou Q, Riedel ER, Carlson DL, Schoder H, Farooki A, Fornier M, Halpern JL, Tunick SJ, Huryn JM: Osteonecrosis of the maxilla and mandible in patients with advanced cancer treated with bisphosphonate therapy. Oncologist 2008;13:911–920.

82 Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, Cui J, Adamus A, Gagel RF, Hortobagyi GN: Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 2008;23:826–836.

83 Migliorati CA, Siegel MA, Elting LS: Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. Lancet Oncol 2006;7:508–514.

84 Weitzman R, Sauter N, Eriksen EF, Tarassoff PG, Lacerna LV, Dias R, Altmeyer A, Csermak-Renner K, McGrath L, Lantwicki L, Hohneker JA: Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients – May 2006. Crit Rev Oncol Hematol 2007;62:148–152.

85 Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, Koutsoukou V, Gika D, Anagnostopoulos A, Papadimitriou C, Terpos E, Dimopoulos MA: Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 2005;23:8580–8587.

86 Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, Fenton R, Gahres N, Sausville E, Ord R, Meiller T: Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol 2006;24:945–952.

87 Lipton A: The safety of zoledronic acid. Expert Opin Drug Saf 2007;6:305–313.

88 Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, Richardson GE, Siena S, Maroto P, Clemens M, Bilynskyy B, Charu V, Beuzeboc P, Rader M, Viniegra M, Saad F, Ke C, Braun A, Jun S: Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 2012;48:3082–3092.