Bone-Targeted Agents

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In the last two decades, bisphosphonates and denosumab have been instrumental in the treatment of patients suffering with prostatic cancer bone metastases [17]. Recently abiraterone and enzalutamide have demonstrated potential beneficial effects on bone metabolism delaying and reducing skeletal complications. Even with recent improvements in medical treatment of skeletal metastases in prostate cancer, the development of effective and precise therapies aimed to improve patients' prognosis and quality of life remains a clinical challenge.

15.1 Bisphosphonates

Bisphosphonates are well established as successful agents for the management of osteoporosis as well as bone metastases in patients with solid cancer and multiple myeloma [38].

Bisphosphonates are analogues of pyrophosphate with a strong affinity for divalent metal ions, such as calcium ions, and for the skeleton. Indeed bisphosphonates are incorporated into bone matrix by binding to exposed hydroxyapatite crystals that provide a barrier to osteoclast-mediated bone resorption and have direct inhibitory effects on osteoblasts. In particular, bisphosphonates are embedded in bone at active remodeling sites, are released in the acidic environment of the resorption lacunae under active osteoclasts, and are taken up by them. There are two classes of bisphosphonates, non-nitrogen-containing and nitrogen-containing bisphosphonates (N-BPs). The nitrogen-containing bisphosphonates (alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid) are more potent osteoclast inhibitors than are non-nitrogen-containing bisphosphonates (e.g., clodronate, etidronate, and tiludronate) [28]. Moreover, nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphatase, an enzyme responsible for the prenylation of GTPases that are essential for osteoclast function, structural integrity, and the prevention of apoptosis [28, 31, 56]. The inhibition of farnesyl pyrophosphatase also results in the accumulation of isopentenyl diphosphate that is incorporated into a cytotoxic nucleotide metabolite, ApppI [31]. Therefore, bisphosphonates affect osteoclast differentiation and maturation and thereby act as potent inhibitors of bone resorption (Fig. 15.1). Preclinical evidence demonstrated that bisphosphonates do not affect only the bone microenvironment but have also a direct effect on macrophages, gamma

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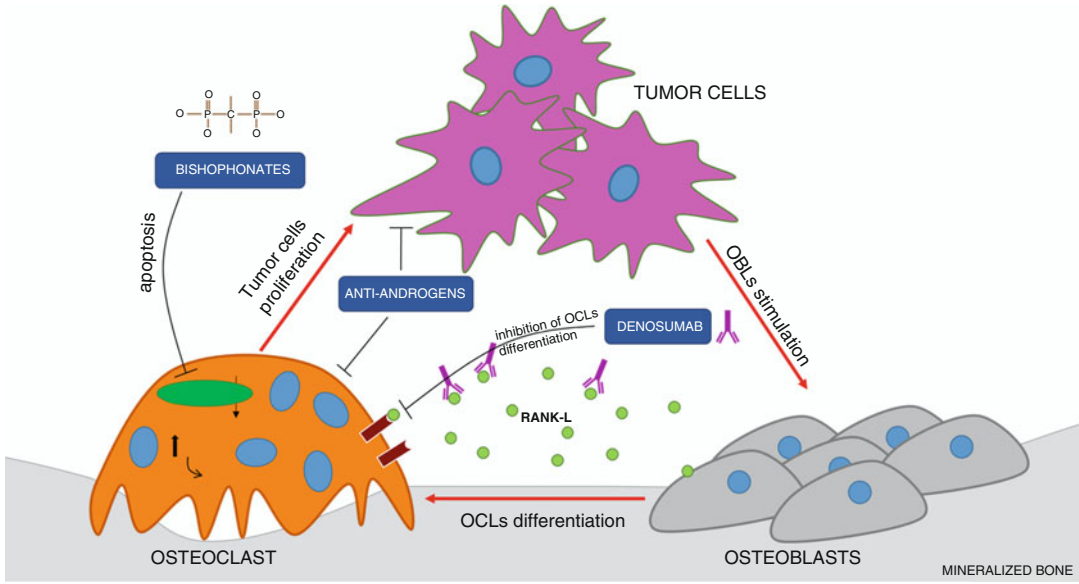

Fig 15.1 Mechanism of action of bisphosphonate, denosumab, and anti-androgen on the bone metastases "vicious cycle." *OCLs* osteoclasts, *OBLs* osteoblasts

delta T cells, osteoblasts, and cancer cells showing antitumor and/or antiangiogenic effects [6].

The efficacy of bisphosphonate treatment on patients with bone metastatic cancer depends on the specific bisphosphonate and on the administered doses (Table 15.1). In a combined analysis of two placebo-controlled studies of 378 men with metastatic prostate cancer, pamidronate (90 mg every 3–4 weeks) failed to demonstrate a significant overall treatment benefit compared to placebo in terms of reduction of SREs and palliation of bone pain [50]. In particular, Small et al. did not observe sustained or significant differences between the pamidronate and placebo groups for self-reported pain, analgesic use, or mobility [50]. In a double-blind placebo-controlled randomized trial, clodronate did not improve bone progression-free survival (BPFS) among men with bone metastases from prostate cancer. Heidenreich A et al. showed that clodronate treatment (300 mg for 8 days) of painful osseous metastases due to hormone-refractory prostate cancer resulted in a significant pain decrease with a concomitant reduction in the daily consumption of analgesics in 75 % of patients [16]. Similarly, ibandronate (6 mg over 1 h each day for 3 days followed by a single infusion of 6 mg every 4 weeks) showed a significant improvement in bone pain in patients with hormone-refractory prostate cancer and bone metastases [15]. Zoledronic acid is the most potent bisphosphonate currently used in men with bone metastatic prostate cancer that has progressed after initial hormone therapy. The benefit of zoledronic acid (4 mg every 3 weeks) was demonstrated in a randomized, placebo-controlled trial in patients with hormone-refractory metastatic prostate carcinoma. This study showed a significant reduction in the frequency of SREs, a longer median time to develop SREs, and lower pain and analgesic scores [44]. In particular, a greater proportion of patients who received placebo had SREs than those who received zoledronic acid at 4 mg (44.2 % versus 33.2 %); median time to first SRE was 321 days for patients who received placebo and was not reached for patients who received zoledronic acid at 4 mg. In a subsequent placebo-controlled randomized clinical trial, zoledronic acid reduced the incidence of SREs (38 % versus 49 % for the placebo group) in men with hormone-refractory metastatic prostate cancer. Moreover, zoledronic acid increased the median time to the first SRE (488 days versus 321 days in the placebo group)

Table 15.1 Summary of main randomized controlled trials evaluating in men with prostate cancer

N° of patients/primary cancer	Scheduling	Study	Results	References
Clodronate				
Hormone refractory metastatic prostate cancer	3 mg i.v. for 8 days	Open, uncontrolled study	Significant decrease in bone pain score in 75 % of patients ($p < 0.001$)	8
Ibandronate				
Hormone refractory metastatic prostate cancer	6 mg i.v. on days 1-3 then 6 mg every 4 weeks	Open, uncontrolled study	92 % of patients had significant pain reduction, and 39 % of patients were completely pain free	9
Pamidronate				
Hormone refractory metastatic prostate cancer	90 mg i.v. every 3 weeks for 27 weeks	Double-bind, placebo-controlled trial	No significant or sustained effect o pain score	7
Zoledronic acid				
Hormone refractory metastatic prostate cancer	4 or 8 mg i.v every 3 weeks for 15 months	Double-bind, placebo-controlled trail	SRE incidence reduction (44.2 % placebo group vs 33.2 % ZA group) and significant decrease in bone pain and analgesic use	10
Hormone refractory metastatic prostate cancer	4 or 8 mg i.v every 3 weeks for 15 months	Double-bind, placebo-controlled trail	SRE incidence reduction (38 % placebo group vs 49 % ZA group) and median time to first SRE increase (321 days placebo group vs 488 days ZA group)	11
Nonmetastatic prostate cancer	4 mg i.v. every 6 months	Randomized placebo-controlled trial	BMD improvement in ZA group compared to placebo: lumbar spine (6 % vs 5 %), left total hip (1 % vs 8 %) and left femoral neck (3 % vs 8 %)	12
Nonmetastaticprostate cancer	4 mg i.v. only in day 1	Randomized controlled trial	BMD improvement in ZA group compared to placebo in lumbar spine and in total hip	13
Nonmetastatic prostate cancer	4 mg i.v. every 3 months	Randomized controlled trial	BMD improvement in ZA group compared to placebo in lumbar spine, femoral neck, and in trochanter and total hip	14

(continued)

Table 15.1 (continued)

N° of patients/primary cancer	Scheduling	Study	Results	References
High-risk, locally advanced, metastatic or recurrent prostate cancer	4 mg for six 3-weekly cycles, then 4-weekly in combination with docetaxel 75 mg/ml (six 3-weekly cycles) + prednisolone 10 mg daily	Randomized controlled trial	No improvement in overall survival in ZA group or delay in SRE	15
Castration-sensitive metastatic prostate cancer	4 mg i.v. every 4 weeks	Double-bind, placebo-controlled trial	Early ZA treatment did not increase time to first SRE (median time 31 months in ZA group vs 29,8 months in placebo group)	16

ZA zoledronic acid, *BMD* bone mineral density, *SRE* skeletal-related event

and reduced the ongoing risk of SREs by 36 % compared with placebo [45]. Further evidence of zoledronic acid efficacy in preventing bone fractures was demonstrated in a randomized phase III trial (RTOG 0518) in patients with high-grade and/or locally advanced, nonmetastatic prostate adenocarcinoma receiving luteinizing hormone-releasing hormone (LHRH) agonist and radiotherapy (RT). Data showed that zoledronic acid treatment was associated with improved bone mineral density (BMD) [21]. Similar results were obtained in another study that showed an increase in BMD and a durable suppression of serum N-telopeptide levels for 12 months in men receiving a gonadotropin-releasing hormone (GnRH) agonist in combination with zoledronic acid [29].

In the adjuvant setting of hormone-sensitive prostate cancer, zoledronic acid can be given to prevent and treat tumor therapy-induced bone loss. A randomized phase III trial demonstrated that this agent increased bone density in patients with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) [51]. Data showed that lumbar spine bone mineral density increased 5.6 % from baseline in 1 year in the zoledronic acid group and decreased 2.2 % in the placebo group (mean difference 7.8 %). Bone mineral density significantly increased from baseline also in the femoral neck, trochanter, and total hip [51]. Currently, the key question is what is the role of zoledronic acid in hormone-sensitive prostate cancer? In the STAMPEDE trial, the addition of zoledronic acid to docetaxel did not improve survival outcomes or delay the SRE incidence [20]. In the CALGB/ALLIANCE 90202 study comparing early treatment in hormone-sensitive prostate cancer versus delayed treatment in castration-resistant prostate cancer (CRPC), no difference in SRE-free survival and no change in survival outcomes were noted. Thus, zoledronic acid did not improve SRE in hormone-sensitive disease (median time to first SRE was 31.9 months in the zoledronic acid group and 29.8 months in the placebo group) [53].

15.2 Denosumab

Bone metabolism is a dynamic process that balances bone formation and bone resorption. Bone resorption is performed by active osteoclasts, while bone formation implies inhibition of bone-resorbing activity and stimulation of osteoblast bone deposition [25]. The receptor activators of nuclear factor-kappaB ligand (RANKL)/RANK/osteoprotegerin (OPG) are members of the TNF and TNF-receptor superfamily and act as essential

mediators of OCL formation, function, and survival. RANKL normally secreted by osteoblast binds to its receptor RANK, which is expressed by precursors and mature osteoclasts, stimulating bone resorption activity; in contrast, OPG, the decoy receptor for RANKL, prevents osteoclast activation [10]. In addition to its role as a regulator of bone remodeling, the RANKL/RANK/OPG network also has a key role in osteolytic bone metastasis [10]. The morphometric analysis of immunohistochemical staining showed that RANK, OPG, and RANKL were not significantly expressed in hyperplastic prostate, while their expression levels were increased 50, 45, and 52.5 %, respectively, in prostate cancer tissue [23]. Understanding the molecular mechanisms that trigger the vicious cycle of bone metastases has provided potential targets such as the RANKL/RANK pathway. It has proven to be an effective target for translational research due to its central role in the cascade of events leading to metastatic bone disease. Indeed it has been demonstrated that RANK expression level in the primary tumor correlated with the occurrence of bone metastases, and RANK-expressing cancer could be found in up to 80 % of bone metastases originating from solid tumors [27, 47], suggesting that RANK enables cancer cells to migrate to bone where RANKL is abundantly expressed by osteoblasts. Furthermore, RANKL was also able to directly induce prostate cancer cell proliferation increasing this vicious cycle [30] (Fig. 15.1). Recent evidence suggests an important role for RANKL/RANK in the immune system including in lymph node development, lymphocyte differentiation, dendritic cell survival, T-cell activation, and tolerance induction.

Denosumab (AMG162) is a human non-cytotoxic IgG2 monoclonal antibody with an extremely high affinity and specificity for human RANKL. It is approved for the treatment of osteoporosis, cancer treatment-induced bone loss, bone metastases, and other skeletal pathologies mediated by osteoclasts [22]. Several clinical trials demonstrated the ability of denosumab to prevent the development of bone metastasis in high-risk prostate cancer patients (Table 15.2).

In a randomized double-blind phase III study of castration-resistant prostate cancer patients with bone metastases, the median time to first SRE for the denosumab arm was significantly prolonged (21 months) compared to the zoledronic acid arm (17 months) with no improvement in OS or progression of disease [12]. In particular, 1904 patients were randomly assigned to treatment, of whom 951 received zoledronic acid and 950 received denosumab. Denosumab significantly delayed the time to first on-study skeletal-related event by 18 % compared with zoledronic acid, with a between-group difference of 3.6 months. Overall survival and investigator-reported disease progression were not significantly different between treatment groups [12]. In another phase III trial, 1432 men with nonmetastatic castration-resistant prostate cancer were randomly assigned to denosumab or placebo. Denosumab increased the time to development of first bone metastasis by a median of 4.2 months compared with placebo, in a population of men deemed to be at high risk for the development of metastatic disease (baseline PSA value ≥8.0 ng/mL and/or PSA doubling time (PSADT) ≤10.0 months). No difference in OS was noted (median 44 versus 45 months; HR, 1.01) [55]. To determine the efficacy of denosumab in men at greatest risk for bone metastases, the researchers evaluated bone-metastasis-free survival (BMFS) in a subset of men with PSADT ≤6 months. Median BMFS in the placebo group of men with PSADT ≤6 months was 6.5 months shorter than for the placebo group (18.7 months versus 25.2 months) [55].

It has been demonstrated that denosumab prevented bone loss in men at high risk for fractures receiving ADT for nonmetastatic prostate cancer [52, 54]. In a phase III study, it was found that denosumab is able to decrease the incidence of new vertebral fractures at 12, 24, and 36 months. The cumulative incidence of new vertebral fractures at 36 months was 3.9 % in the placebo group and 1.5 % in the denosumab group with a significant decrease of 62 %. This drop was significant even at 12 months (1.9 for placebo versus 0.3 for denosumab) and 24 months (3.3 for placebo versus 1.0 for denosumab) [52, 54].

Table 15.2 Summary of main randomized controlled trials evaluating denosumab in men with prostate cancer

N° of patients/primary cancer	Scheduling	Study	Results	References
Denosumab				
Bone metastatic castration resistant prostate cancer	120 mg subcutaneous denosumab plus intravenous placebo, or 4 mg intravenous zoledronic acid plus subcutaneous placebo every 4 weeks	Multicenter, double-blind study, randomized	Median time to first SRE was 20.7 months with denosumab compared with 17.1 months with zoledronic acid	24
Nonmetastatic castration resistant prostate cancer	Denosumab 120 mg or subcutaneous placebo every 4 weeks	Double-blind, randomized, placebo-controlled study	Denosumab significantly increased bone-metastasis-free survival by a median of 4.2 months compared with placebo	25
Nonmetastatic hormone-sensitive prostate cancer receiving androgen-deprivation therapy (ADT)	Denosumab at a dose of 60 mg subcutaneously every 6 months or placebo	Double-bind, multicenter study	BMD of the lumbar spine had increased by 5.6 % in the denosumab group as compared with a loss of 1.0 % in the placebo group	26

BMD bone mineral density, *SRE* skeletal-related event

15.3 Safety of Bone Target Therapies

One of the most commonly reported adverse events related to bisphosphonates and denosumab treatment is hypocalcemia that is most often asymptomatic with these agents [17]. In particular, hypocalcemia occurred more frequently with denosumab than with zoledronic acid as shown in the phase III trial in patients with CRPC and bone metastases (13 % versus 6 %, $p<0.0001$) [12]. In an integrated analysis of 5723 patients from three randomized phase III trials, the safety profile for denosumab was better than for zoledronic acid, demonstrating no effect on renal function and no need for dose adjustment or renal monitoring [24]. In patients receiving zoledronic acid, the incidence of hypocalcemia was lower than in patients receiving denosumab (1.3 % versus 3.1 % for grade 3 or grade 4 toxicities), though most cases were asymptomatic [24]. Thus, repletion of vitamin D levels before and during the therapy and monitoring of calcium levels during therapy are recommended in the prescribing information of denosumab [18].

15.4 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) is a relatively uncommon but potentially serious adverse event reported in patients treated with antiresorptive agents such as bisphosphonates (BPs) and the RANKL inhibitor denosumab [43]. The reported incidence of ONJ is 1.2–9.9 % (mostly derived from retrospective analyses) with pooled risk estimated incidence, in BPs users of 2.4 % [37]. In RCTs comparing zoledronic acid and denosumab in 5677 patients who underwent screening dental procedure, 89 ONJ cases were reported, of which 52 are in the denosumab group [43]. ONJ was defined as the persistence of exposed bone in the oral cavity, despite an adequate treatment for

6 weeks, without local evidence of malignancy and no prior RT to the affected region [41]. However, ONJ may present with the nonexposed variant of ONJ. Recently Fedele et al. [11] performed a secondary analysis of data from MISSION, a cross-sectional study of a large population of patients with bisphosphonate-associated ONJ recruited in 13 European centers [3]. A total of 886 consecutive patients were recruited and 799 were studied after data cleaning. Of these, 607 (76 %) were diagnosed according to the traditional definition. Diagnosis in the remaining 192 (24 %) could not be adjudicated as they had several abnormal features relating to the jaws but no visible necrotic bone. The groups were similar for most of the phenotypic variables tested. Thus the authors showed that the use of the traditional definition may result in one quarter of patients remaining undiagnosed. The American Association of Oral and Maxillofacial Surgeons (AAOMS) recommend the term medical-related osteonecrosis of the jaw (MRONJ) as preferred [39] because of the recognition of jaw necrosis as a complication of other drugs including the RANK ligand inhibitor denosumab and antiangiogenic agents. Table 15.1 shows the MRONJ staging [39]. Among the risk factors, we must consider the presence of chronic periodontal pathologies; poor oral hygiene; use, duration, and type of BP therapy or denosumab; oral infections; dental caries; tooth extractions; use of dental appliances; denture traumatisms; fractures; invasive dental surgery during the course of BP therapy; concurrent disease (e.g., diabetes, peripheral vasculopathy); and presence of anemia [39, 41]. In a retrospective study on 567 cases with ONJ, [57] found that, in 205 of them (36.2 %), no invasive procedure was performed. MRONJ is linked to concomitant use of different drugs such as chemotherapy, antiretrovirals, steroids, thalidomide, bevacizumab, docetaxel, TKI sunitinib or sorafenib, and anthracyclines [5]. The role of genetic factors is receiving increased attention [32].

ONJ may be asymptomatic for weeks or months. Lesions become symptomatic when there is associated inflammation of surrounding soft tissues, infection, and loosening of teeth drainage and when exposed bone produces trauma to adjacent soft tissues (cutaneous fistula, mucosal fistula, bone exposed through the skin). Preventive dental measures, after dental screening examination [1, 7, 40, 41, 59], are advocated to reduce the ONJ incidence [9, 29, 37] due to their efficacy in patients with bone metastases. Active oral infections should be treated, and sites at high risk for infection should be eliminated. Oral care should be provided by a dentist or dental professional who is familiar with cancer therapy. Patient education on the importance of oral hygiene, the regular dental evaluation, and the risk of ONJ is paramount. Treatment of MRONJ is based on a conservative therapy with limited debridement, oral antibiotics, oral rinsed with chlorhexidine or hydrogen peroxide, antibacterial mouth rinse, and pain control. Major surgery is indicated after the formation of necrotic bone sequestrum. Total sequestration of necrotic bone was obtained in ten patients with ONJ lesions $\leq$2.5 cm treated with topical application of an oil suspension enriched with medical 03 gas after the failure of various cycles of antibiotics [35]. No patient required surgical intervention. In another open-label prospective study, [36] evaluated the efficacy and tolerability of medical ozone (03) treatment delivered as gas insufflation on each ONJ lesion >2.5 cm developed in 24 patients treated with zoledronic acid after failure of various antibiotics. Six patients had the sequestrum and spontaneous expulsion of the necrotic bone followed by oral mucosa re-epithelization. In 12 patients with the largest and deeper ONJ lesions, 03 gas therapy produced the sequestrum of the necrotic bone after 10–38 insufflations; surgery was necessary to remove it in 11 patients. Removal was possible without the resection of healthy mandible edge because of the presence of bone sequestrum. No adverse event was reported and no ONJ relapse appeared. There are reports that low-level laser therapy improves healing and symptoms related to ONJ [49, 58]. Future research is required to better understand the individualized treatment of ONJ in cancer patients as well as in patients with osteoporosis.

American Association of Oral and Maxillofacial Surgeons (AAOMS) medication-related ONJ (MRONJ) staging

ONJ staging	Characteristics
At risk	No apparent necrotic bone in patients who have been treated with antiresorptive therapy
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes and symptoms
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone, in asymptomatic patients without evidence of infection
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in region of exposed bone ± purulent drainage
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and 1+ complication*

*Exposed and necrotic bone extending beyond the region of alveolar bone resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor.

Ruggiero SL, et al. J Oral Maxillofac Surg 2014;72:1938–56.

15.5 Other Molecules

Several molecules that are under intensive clinical testing on humans, although they target directly the tumor cell and not the bone microenvironment, have demonstrated over an improved survival, of being able to modify the natural history of bone metastases, resulting in a delay of the occurrence of SRE, a reduction of bone pain, and an improvement in quality of life. These therapeutic options include abiraterone and enzalutamide.

15.5.1 Abiraterone

Abiraterone acetate (ABI) (Zytiga, Janssen) is a selective inhibitor of androgen biosynthesis; it acts potently and irreversibly blocks Cyp17 resulting in virtually undetectable serum and intratumoral androgen production in the adrenals, testes, and prostate cancer cells [2, 33]. ABI is currently approved in both pre- and post-docetaxel setting of mCRPC.

In phase III studies in metastatic castration-resistant prostate cancer (mCRPC) patients, it was demonstrated that ABI treatment is associated not only with a significant survival advantage in both chemotherapy-naive and chemotherapy-treated patients but also, in docetaxel treated patients, with a better pain control from skeletal metastases and a delay in time to development SREs and in radiological skeletal progression [7, 13, 14, 26, 42].

In particular, in the pivotal study COU-301, involving patients with metastatic castration-resistant prostate cancer who previously received chemotherapy, De Bono showed an improvement in overall survival in the abiraterone with prednisone arm (14.8 months) versus the prednisone-only treated patients' group (10.9 months), with a 35 % reduction in the risk of death in the abiraterone arm [8]. In addition, abiraterone acetate and prednisone offer effective pain relief, delayed pain progression, and prevention of skeletal-related events compared with prednisone alone. Indeed, 25 % of patients developed a skeletal event in 9.9 months when treated with abiraterone and 4.9 months with placebo, and the median time to occurrence of first SRE was 25.0 months with abiraterone compared to 20.3 months with placebo [7, 13, 14]. In addition, in patients with

clinically significant pain at baseline, abiraterone acetate and prednisone offer effective pain relief and delayed pain progression. Indeed, in patients with significant pain at baseline, abiraterone acetate and prednisone obtained a more significative palliation in 157 of 349 (45.0 %) of patients versus 47 of 163 (28.8 %) in those who did not receive abiraterone and faster palliation (median time to palliation 5.6 months versus 13.7 months) of pain intensity than did prednisone only [26].

In the COU-302 trial, abiraterone acetate plus prednisone before docetaxel was shown to yield a significant improvement in radiographic progression-free survival associated with a trend toward improved overall survival [42].

An interim analysis of the COU-302 study confirmed that patients treated with abiraterone showed a statistically significant improvement in rPFS (HR 0.52; $p < 0.0001$). The overall survival (OS) analysis favored abiraterone over prednisone alone (median 35.3 versus 30.1 months), and the OS benefit of abiraterone was supported in an exploratory multivariate analysis (HR 0.74; $p = 0.0017$) that adjusted for baseline prognostic factor. In addition, analyses of prespecified measures of patient-reported outcomes confirmed that abiraterone treatment delayed pain progression and deterioration in functional status compared with prednisone alone [34].

Finally a more recent post hoc analysis [46] of study COU-AA-302 demonstrated that treatment with abiraterone acetate and prednisone with concomitant bone-targeted therapy (BTT; zoledronic acid (93 %), denosumab (6 %), and other BTTs (1 %)) for treatment of bone metastases was safe and well tolerated and that the efficacy of abiraterone is maintained with concomitant BTT, with a possible added benefit of delaying the need for opiates to control pain. In this analysis, the comparisons among all patient groups favored abiraterone over prednisone alone, and concomitant BTT was associated with increased effectiveness of abiraterone regarding clinical outcomes. In particular, among patients treated with abiraterone, BTT was associated with a longer time to ECOG PS deterioration. Abiraterone in combination with BTT, compared with prednisone with BTT, delayed the median time to deterioration in ECOG PS by 3.9 months. These findings confirm the efficacy of abiraterone plus BTT combination in clinical practice. In conclusion, it is reasonable to speculate that the ABI effects on metastatic bone disease may be secondary to a systemic control of the disease due to a direct antitumor effect that, in turn, leads to a decrease of cancer cells/OCLs/OBLs vicious circle or, alternatively, to a specific action directed to bone microenvironment [19] (Fig. 15.1).

15.5.2 Enzalutamide

Other new drugs are being tested in metastatic prostate cancer with potential therapeutic effect even on bone metastases (enzalutamide, cabozantinib, etc.). In particular, enzalutamide (formerly MDV3100, trade name XTANDI™, Astellas) is a latest-generation drug able to bind the androgen receptor, to prevent its translocation within the nucleus and its deregulatory function on DNA, and currently approved for the treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC).

The AFFIRM study evaluated enzalutamide in men with mCRPC who had previously received docetaxel [13, 14, 48]. This trial has demonstrated that enzalutamide increases survival with a median of 18.4 months versus 13.6 months in the placebo group.

A subanalysis of AFFIRM trial [13, 14] focused on the effect of enzalutamide versus placebo on SRE, pain, and QOL. The subanalysis showed that enzalutamide significantly retard SREs with delayed time to the first SRE at 16.7 months versus 13.3 months in those who received placebo, representing a 31 % reduction in risk of SRE ($P = .0001$). The distribution of first SRE showed a generally favorable effect of enzalutamide, with fewer patients experiencing radiation to the bone (20 % for enzalutamide versus 25 % for placebo) and spinal cord compression (6 % versus 8 %), but about 4 % in each group experiencing pathological fracture. In addition, all parameters of pain palliation, includ-

ing time to pain progression, mean reduction in pain intensity, and reduction in pain interference with daily activity, were all in favor of the enzalutamide compared to the placebo arm.

More recently, the mCRPC chemo-naive patients were investigated in a new phase III trial; the PREVAIL trial aimed to evaluate enzalutamide in men with chemo-naïve mCRPC that had progressed despite the use of androgen deprivation therapy (ADT) (luteinizing hormone-releasing hormone analogue or orchiectomy) [4]. The study demonstrated a statistically significant delay in the growth or spread of metastatic prostate cancer, a reduction in the risk of death, and a delay of the time to initiation of chemotherapy compared with the placebo arm. More in detail, the results showed a reduction of risk of radiographic progression or death by 81 % (HR = 0.19; $p < 0.0001$), compared with placebo and a rate of radiographic progression-free survival at 12 months of follow-up of 65 % among patients treated with enzalutamide versus 14 % among patients receiving placebo.

The secondary endpoint of the study included the time until the initiation of cytotoxic chemotherapy, the time until the first skeletal-related event, the best overall soft-tissue response, the time until PSA progression, and a decline in the PSA level of 50 % or more from baseline; the results showed the superiority of enzalutamide over placebo with respect to all the prespecified endpoints. The median time until the initiation of cytotoxic chemotherapy was 28 months in the enzalutamide group versus 10.8 months in the placebo group. Treatment with enzalutamide also resulted in a reduction in the risk of a first SRE; indeed at a median of approximately 31 months, the SRE occurred in 32 % of patients in the enzalutamide group and in 37 % in the placebo group.

Enzalutamide was also superior to placebo with respect to the time until a decline in the quality of life. The median time until a quality-of-life deterioration, as measured on the FACT-P scale, was 11.3 months in the enzalutamide group and 5.6 months in the placebo group.

References

1. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons (2007) American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 65:369–376
2. Barrie SE, Potter GA, Goddard PM et al (1994) Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17-20 lyase). J Steroid Biochem Mol Biol 50:267–273
3. Bedogni A, Fedele S, Bedogni G et al (2014) Staging of jaw osteonecrosis requires computed tomography for accurate definition of the extent of bony disease. Br J Maxillofac Surg 52:603–608
4. Beer T, Armstrong A, Rathkopf D et al (2014) Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371:424–433
5. Berenson JR, Stopeck AT. Medication-related osteonecrosis of the jaw in patients with cancer. http://www.uptodate.com/contents/medication-related-osteonecrosis-ofthe jaw-in-patients-with-cancer. Accessed on 28 Jan 2016
6. Coleman R, Gnant M, Morgan G et al (2012) Effects of bone-targeted agents on cancer progression and mortality. J Natl Cancer Inst 104:1059–1067
7. Damato K, Gralow J, Hoff A et al (2005) Expert panel recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaws. LDA J 64: 21–24
8. De Bono JS, Logothetis CJ, Molina A et al (2011) Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995–2005
9. Dimopoulos MA, Kastritis E, Bamia C et al (2009) Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. Ann Oncol 20:117–120
10. Dougall WC, Chaisson M (2006) The RANK/RANKL/OPG triad in cancer-induced bone diseases. Cancer Metastasis Rev 25:541–549
11. Fedele S, Bedogni G, Scoletta M et al (2015) Up to a quarter of patients with osteonecrosis of the jaw associated with antiresorptive agents remain undiagnosed. Br J Oral Maxillofac Surg 53:13–17
12. Fizazi K, Carducci M, Smith M et al (2011) Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 377:813–822
13. Fizazi K, Scher HI, Molina A et al (2012) Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 13:983–992
14. Fizazi K, Scher HI, Saad F et al (2012) Impact of Enzalutamide, an androgen receptor signaling inhibitor, on time to first skeletal related event (SRE) and

pain in the phase 3 AFFIRM Study. Ann Oncol 23 abstract 8960
15. Heidenreich A, Elert A, Hofmann R (2002) Ibandronate in the treatment of prostate cancer associated painful osseous metastases. Prostate Cancer Prostatic Dis 5:231–235
16. Heidenreich A, Hofmann R, Engelmann UH (2001) The use of bisphosphonate for the palliative treatment of painful bone metastasis due to hormone refractory prostate cancer. J Urol 165:136–140
17. Horwich A, Parker C, de Reijke T et al (2013) Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24: 106–114
18. Iranikhah M, Stricker S, Freeman MK (2014) Future of bisphosphonates and denosumab for men with advanced prostate cancer. Cancer Manag Res 6: 217–224
19. Iuliani M, Pantano F, Buttigliero C et al (2015) Biological and clinical effects of abiraterone on antiresorptive and anabolic activity in bone microenvironment. Oncotarget 6:12520–12528
20. James ND, Sydes MR, Clarke NW et al (2015) STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 387(10024):1163–1177
21. Kachnic LA, Pugh SL, Tai P et al (2013) RTOG 0518: randomized phase III trial to evaluate zoledronic acid for prevention of osteoporosis and associated fractures in prostate cancer patients. Prostate Cancer Prostatic Dis 16:382–386
22. Lacey DL, Boyle WJ, Simonet WS et al (2012) Bench to bedside: elucidation of the OPG-RANK-RANKL pathway and the development of denosumab. Nat Rev Drug Discov 11:401–419
23. Li X, Liu Y, Wu B et al (2014) Potential role of the OPG/RANK/RANKL axis in prostate cancer invasion and bone metastasis. Oncol Rep 32:2605–2611
24. Lipton A, Fizazi K, Stopeck AT et al (2012) 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 48:3082–3092
25. Liu XH, Kirschenbaum A, Yao S et al (2005) Cross-talk between the interleukin-6 and prostaglandin E(2) signaling systems results in enhancement of osteoclastogenesis through effects on the osteoprotegerin/receptor activator of nuclear factor-{kappa}B (RANK) ligand/RANK system. Endocrinology 146:1991–1998
26. Logothetis CJ, Basch E, Molina A et al (2012) Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol 13:1210–1217
27. Loser K, Mehling A, Loeser S et al (2006) Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. Nat Med 12:1372–1379
28. Luckman SP, Hughes DE, Coxon FP et al (1998) Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. J Bone Miner Res 13:581–589
29. Michaelson MD, Kaufman DS, Lee H et al (2007) Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol 25(9):1038–1042
30. Miller RE, Roudier M, Jones J et al (2008) RANK ligand inhibition plus docetaxel improves survival and reduces tumor burden in a murine model of prostate cancer bone metastasis. Mol Cancer Ther 7(7): 2160–2169
31. Mönkkönen H, Auriola S, Lehenkari P et al (2006) A new endogenous ATP analog (ApppI) inhibits the mitochondrial adenine nucleotide translocase (ANT) and is responsible for the apoptosis induced by nitrogen-containing bisphosphonates. Br J Pharmacol 147:437–445
32. Nicoletti P, Cartsos VM, Palaska PK et al (2012) Genomewide pharmacogenetics of bisphosphonate-induced osteonecrosis of the jaw: the role of RBMS3. Oncologist 17:279
33. O'Donnell A, Judson I, Dowsett M et al (2004) Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer 90:2317–2325
34. Rathkopf DE, Smith MR, de Bono JS et al (2014) Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol 66:815–825
35. Ripamonti CI, Cislaghi E, Mariani L et al (2011) Efficacy and safety of medical ozone (03) delivered in oil suspension applications for the treatment of osteonecrosis of the jaw in patients with bone metastases treated with bisphosphonates: Preliminary results of a phase I-II study. Oral Oncol 47:185–190
36. Ripamonti CI, Maniezzo M, Boldini S et al (2012) Efficacy and tolerability of medical ozone gas insufflations in patients with osteonecrosis of the jaw treated with bisphosphonates-Preliminary data. Med Ozone Gas Insufflat Treat ONJ Lesions J Bone Oncol 1:81–87
37. Ripamonti CI, Maniezzo M, Campa T et al (2009) Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumor patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milano. Ann Oncol 20(1):137–145
38. Roelofs AJ, Thompson K, Gordon S et al (2006) Molecular mechanisms of action of bisphosphonates: current status. Clin Cancer Res 12:6222s–6230s

39. Ruggiero RL et al (2014) American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw-2014 update. J Oral Maxillofac Surg 72/10:1938–1956
40. Ruggiero S, Gralow J, Marx RE et al (2006) Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Pract 2(1):7–14
41. Ruggiero SL, Dodson TB, Assael LA et al (2009) American Association of oral and maxillofacial surgeons position paper on bisphosphonate-related osteonecrosis of the jaw-2009 update. J Oral Maxillofac Surg 67(Suppl 5):2–12
42. Ryan CJ, Smith MR, de Bono JS et al (2013) Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138–148
43. Saad F, Brown JE, Poznack V et al (2012) Incidence, risk factors, and outcome of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 23:1341–1347
44. Saad F, Gleason DM, Murray R et al (2002) A randomized, placebo-controlled trial of zoledronic acid in patients with hormone refractory metastatic prostate carcinoma. J Natl Cancer Inst 94(19):1458–1468
45. Saad F, Gleason DM, Murray R et al (2004) Long term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone refractory prostate carcinoma. J Natl Cancer Inst 96(11):879–882
46. Saad F, Shore N, Van Poppel H et al (2015) Impact of bone-targeted therapies in chemotherapy-naïve metastatic castration-resistant prostate cancer patients treated with abiraterone acetate: post hoc analysis of study COU-AA-302. Eur Urol 68(4):570–577
47. Santini D, Perrone G, Roato I et al (2011) Expression pattern of receptor activator of NFkB (RANK) in a series of primary solid tumors and related bone metastases. J Cell Physiol 226:780–784
48. Scher HI, Fizazi K, Saad F et al; AFFIRM Investigators (2012) Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367(13):1187–1197
49. Scoletta M, Arduino PG, Reggio L et al (2010) Effect of low-level laser irradiation on bisphosphonate-induced osteonecrosis of the jaws: preliminary results of a prospective study. Photomed Laser Surg 28:179
50. Small EJ, Smith MR, Seaman JJ et al (2003) 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 21:4277e–4284e
51. Smith MR, Eastham J, Gleason DM et al (2003) Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 169(6):2008–2012
52. Smith MR, Egerdie B, Hemdezet TN et al (2009) Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 361:745–755
53. Smith MR, Halabi S, Ryan CJ et al (2014) Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (Alliance). J Clin Oncol 32(11):1143–1150
54. Smith MR, Saad F, Egerdie B et al (2009) Effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer. J Urol 182:2670–2675
55. Smith MR, Saad F, Oudard S et al (2013) Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 31(30):3800–3806
56. Van Beek E, Pieterman E, Cohen L et al (1999) Nitrogen-containing bisphosphonates inhibit isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo. Biochem Biophys Res Commun 255(2):491
57. Vescovi P, Campisi G, Fusco V et al (2011) Surgery-triggered and non surgery-triggered Bisphosphonates-related Osteonecrosis of the Jaws (BRONJ): a retrospective analysis of 567 cases in an Italian multi center study. Oral Oncol 47(3):191–194
58. Vescovi P, Merigo E, Manfredi M et al (2008) Nd:YAG laser biostimulation in the treatment of bisphosphonate-associated osteonecrosis of the jaw: clinical experience in 28 cases. Photomed Laser Surg 26:37
59. Weitzman R, Sauter N, Eriksen EF et al (2007) Critical review: updated recommendations for the prevention, diagnosis and treatment of osteonecrosis of the jaw in cancer patients. Crit Rev Oncol Hematol 62(2):148–152