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Review Article

Current treatments and novel therapeutic targets for castration resistant prostate cancer with bone metastasis

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Abstract: Prostate cancer is a leading cause of cancer death in men in developed countries. While early stage disease can often be cured, many patients eventually develop castration resistant prostate cancer (CRPC). The majority of CRPC patients have bone metastases, which cause significant morbidity and mortality. Although there is no cure for prostate cancer metastatic to bone, several bone-targeted agents have been approved to prevent skeletal-related events (SREs). Among them, bisphosphonates were the first class of drugs investigated for prevention of SREs. Denosumab is a recently approved agent that binds to the receptor activator of nuclear factor-κB ligand (RANKL) as a humanized monoclonal antibody. Both agents target prostate cancer skeletal metastasis through the inhibition of bone resorption. Alpharadin is the first radiopharmaceutical agent that has significant overall survival benefit. It has benefits in pain palliation and SREs as well. Another newly approved drug is Abiraterone acetate, which decreases circulating levels of testosterone by targeting an enzyme expressed in the testis and the adrenal, as well as in prostate cancer tissues. This review outlines the clinical and preclinical data supporting the use of these and new agents in development for CRPC with bone metastasis.

Keywords: CRPC, bone metastasis

Introduction

Prostate cancer (PCa) is the most common malignancy and the second-leading cause of cancer death in American men, with 238,590 new diagnoses and 29,720 deaths estimated in the US in 2013 [1]. PCa patients identified with early stage disease can often be cured with local therapy like prostatectomy or radiation therapy. For more advanced prostate cancer that has spread beyond the prostate gland, androgen-deprivation therapy is commonly used before the prostate cancer becomes castration-resistant. After hormone-deprivation therapy fails, chemotherapeutic are the next option [2]. Docetaxel is the first-line chemotherapy for metastatic castrate resistant PCa. It inhibits cell proliferation, improves overall survival modestly and reduces pain (35% versus 22% in placebo) [3]. However, for metastatic castration-resistant prostate cancer (mCRPC) cases these treatments show little benefit [4]. More than 90% of patients with mCRPC develop bone metastases [5, 6], and most of them are suffering from asymptomatic pain or skeletal-related events (SREs), such as spinal cord compression, and pathological fractures. This review will focus on current and promising therapeutic options specific for this stage of disease. This review will focus on the clinical evidence supporting current and prospective bone-targeted therapies for CRPC.

Treatments target bone-tumor microenvironment

Bisphosphonates

Bisphosphonates are the first class of agents that were investigated for SRE prevention in patients with mCRPC for decades. Osteoporosis is a common consequence of androgen depri-

vation therapy for prostate cancer. Up to 20% of patients on androgen deprivation therapy for localized prostate cancer will have a bone fracture within 5 years [7]. Zoledronic acid was the only FDA approved bisphosphonate for the prevention of SREs. Bisphosphonates exert a variety of actions on bone and tumor cells [8, 9]. The best characterized mechanism of bisphosphonates is their function as pyrophosphate analogues, which adhere to hydroxyapatite crystal-binding sites in the bone matrix, attach to the sites in areas of active resorption and prevent osteoclast adherence via inhibiting osteoclast progenitor differentiation and survival through stimulation of osteoblasts [10, 11].

Abnormal osteoblastic and osteoclastic activities in the prostate metastatic bone microenvironment justify the rationale for using bisphosphonate therapy in mCRPC. In a randomized, placebo-controlled trial, patients with mCRPC were randomly grouped and received intravenous zoledronic acid at 4 mg, 8 mg, or placebo every 3 weeks for 22 cycles [12]. A reduced proportion of SREs in patients who received zoledronic acid at 4 mg (44.2% versus 33.2% in placebo; P=0.021) were observed. Meanwhile, no significant difference in overall survival, disease progression, performance status, or quality of life was observed among the groups. At a follow-up of 24 months, patients in the zolendronic acid group continued to demonstrate decreased bone pain, and prolonged time to first SRE (488 days in the treatment group versus 321 in the control, P=0.009) [13].

Disappointingly, subsequent studies of other bisphosphonates, such as pamidronate and clodronate, have not yielded similar results [14, 15]. Adverse effects including fatigue, anemia, myalgia, fever, and lower extremity edema were more common in the bisphosphonate-treated patients than in controls. The identification of cases of osteonecrosis of the jaw, an incredibly rare condition in patient not receiving bisphosphonate therapy, has also raised concern in the medical community regarding the possible adverse reactions of this class of medications, in spite of its positive effects [16, 17]. A best practice guidelines of using bisphosphonates in mCRPC patients will help to balance its undisputed benefits with the increasingly safety concerns.

Liposomes-improved drug delivery

Targeted drug delivery systems like liposomes may help overcome drug resistance by achieving higher drug levels at the tumor site. In addition, targeted drug delivery can leading to fewere systemic side effects by limitingthe exposure of healthy tissue to drug. In light of the extensive experience with several liposomal anticancer formulations, liposomal targeting of anticancer drugs to tumors in patients with prostate cancer seems a plausible approach [18].

The bone/bone-marrow microenvironment can be exploited to selectively deliver anticancer drugs to bone metastases. Bisphosphonate-coated liposomes may effectively target active bone surfaces (hydroxyapatite), abundantly exposed in the local bone metastatic environment. Tumor-associated macrophages promote tumor growth on active bone surfaces by direct release of growth and inflammatory factors (EGF, VEGF, IL-10, IL-12, TNF-a), while osteoclasts mediate bone resorption, which leads to the release of bone-matrix bound growth factors (TGF-β) [19-21].

Liposomal bisphosphonate zoledronic acid resulted in decreased levels of tumor-associated macrophages, reduced angiogenesis and inhibition of prostate xenograft growth [22]. In metastatic xenograft models, liposomal delivery of clodronate, another bisphosphonate, inhibited metastatic growth and reduced the number of bone metastases through suppressant of tumor-associated macrophages, reduced levels of inflammatory cytokine IL-6 and a reduction of osteoclast activity [23, 24].

Denosumab

Denosumab is a fully humanized monoclonal antibody directed against the receptor activator of nuclear factor-κB ligand (RANKL). In November 2010, it was approved by the FDA for prevention of SREs in patients with bone metastases from solid tumors, including prostate cancer. RANKL is a tumor necrosis family (TNF) member that is expressed on cell surface and is mainly released by osteoblasts and activated T cells. The binding between RANKL and its receptor RANK on osteclast lineage cell surface is essential for the maturation and function of osteoclasts. Upon RANKL binding to

RANK, a serial of signaling pathways are activated to stimulate osteoclast formation, activation, adherence, and survival, which eventually leading to bone resorption [25-28].

Results from a phase II trial of denosumab in cancer patients including bone metastatic CRPC previous exposed to intravenous bisphosphonate therapy, treatment with denosumab showed fewer on-study SREs than those continue receiving intravenous bisphosphonate [29]. To further determine the effects of denosumab in men receiving androgen deprivation therapy for prostate cancer, the HALT prostate cancer trial randomized men to receive denosumab at a dose of 60 mg subcutaneously every 6 months or placebo. At 24 months, patients received denosumab were associated with increased bone mineral density at all sites including lumbar spine, femoral neck, and total hip. Denosumab also reduced the incidence of new vertebral fractures among men receiving androgen deprivation therapy for nonmetastatic prostate cancer [30, 31].

Two randomized, double-blinded phase III clinical trials have been conducted to investigate denosumab efficacy in prostate cancer. One trial compared denosumab with zoledronic acid for prevention of SREs in 1904 men with bone metastases from CRPC demonstrated a more favorable efficacy of denosumab than zoledronic acid [32]. Among the 950 patients assigned to denosumab, the median time to first SREs was 20.7 months compared to 17.1 months in the 951 patients assigned to zoledronic acid. Another study was a placebo-controlled trial designed specifically to gauge bone-metastasis-free survival in men at high risk of developing bone metastasis with PSA ≥8.0 μg/L or PSA doubling time of ≤10.0 months [33]. Though denosumab usage did not show benefit in overall survival, the denosumab-treated arm did demonstrate a longer time to bone-metastases by a median of 4.2 months.

Radiopharmaceuticals

Targeting of the prostate cancer bone metastasis microenvironment is an increasingly common adjunctive strategy in the management of mCRPC. Radiopharmaceuticals differ from other agents used for this purpose based on their nuclear properties, clinical benefit, and toxicity. Radiopharmaceuticals may emit radiation as either alpha or beta particles. An alpha particle is ejected from a heavy nucleus during alpha decay and consists of two neutrons and two protons. A beta particle is an electron released from a nucleus during beta decay which converts a neutron into a proton, an electron, and a neutrino [6]. Both alpha- and beta-particles can send local ionizing radiation to malignant tissue [34]. So far, due to the failure to improve prostate cancer patient survival, current beta-emitting radiopharmaceuticals including strontium-89, 153Sm-EDTMP, and Re-186 HEDP, have been only approved for palliation of pain caused by bone metastases in CRPC patients [35].

Radium-223 chloride (Ra-223, Alpharadin) is the first radiopharmaceutical agent demonstrated an overall survival advantage in CRPC patients with bone metastases. Radium-223 targets sites of bone metastasis via emitting of α-particles which provide more dense ionizing radiation in a narrow range of <100 μm (corresponding to 2-10 tumor cell diameters) [36]. Its short track-length significantly minimize myelotoxicity. A phase III, randomized, double-blind, placebo-controlled study of Ra-223 in men with CRPC and bone metastasis demonstrated a significant improvement in overall survival (14.9 V 11.3 months; P=0.00007) and time to first skeletal-related event (15.6 V 9.8 months; P=0.00037) for patients in the treatment arm [34]. This trial led to alpharadin approval by FDA in 2013 for patients with symptomatic mCRPC to the bones in the absence of visceral metastases. The recommended dose and schedule for using alpharadin is by slow administered intravenously over 1 minute at 1.35 microcuries/kg every 4 weeks for 6 doses.

Immnotherapy

Vaccine Sipuleucel-T

Sipuleucel-T is a cancer vaccine involving the reintroduction of antigen-presenting cells (APC) using the hematopoietic progenitor cells prepared via leukapheresis from patients themselves. A fusing protein consisting prostate acid phosphatase (PAP) conjugated with granulocyte-macrophage colony-stimulating factor (GM-CSF) named PA2024 will be loaded to these APC to stimulate the patient's immune responses against prostate cancer cells. After being infused back into the patient, Sipuleucel-T

specifically recognizes immature cytotoxic T lymphocytes ($CD8^+$ cells) and binds to the surface receptors of T cells first and subsequently provides PAP epitopes to these T lymphocytes which are further directed to mount an immune reaction against prostate cancer cells. Sipuleucel-T also acts a vaccine to activate the helper $CD4^+$ lymphocytes, which are able to directly attack the cancer cells and retain other cytotoxic T lymphocytes via secretion of cytokines. Influenced by the initial white blood cell removal when Sipuleucel-T is prepared, other immune cells, such as T cells, B cells and natural killer cells, can also exist in Sipuleucel-T [37, 38].

One of the prerequisite of Sipuleucel-T therapy is the PAP expression in at least 25% of cancer cells because PAP required as the navigating epitome for this therapy to be effective. This personalized treatment eventually induces humoral and T cell immune response as demonstrated by the augments in IgM and IgG antibodies against PA2024 and PAP. The IgM and IgG antibodies titers exceeding 400 were observed in 66.2% and 28.5% of treated patients. Both IgM and IgG antibodies are around 20-fold higher compared to those ratios in the placebo group. Similarly, in response to PA2024 and PAP, T-cell proliferation was much more frequent in Sipuleucel-T therapy group six weeks after the infusion [39].

Three phase III clinical trials on Sipuleucel-T suggested that it can significantly improve the overall survival of patients. There was a 26.5% reduction in risk of death from prostate cancer, providing 4.1 months improvement (25.8 months versus 21.7 months) in median overall survival. The median time to prostate cancer progressionwith Sipuleucel-T therapy was no different from that of placebo-treated patients [39-41]. In 2010, Sipuleucel-T was approved by the FDA for the treatment of asymptomatic or minimally symptomatic CRPC. However, the average monthly expenditure is $22,683 per month of added median survival with sipuleucel-T [42]. Thus the high therapy costs may restrict Sipuleucel-T as a standard treatment option for CRPC.

Therapy target androgen pathway

CYP17 inhibitor abiraterone

Hormone therapy is based on the observation that up to 80% of prostate cancer cell proliferation is stimulated by androgens [43]. Orchiectomy or administration of GnRH analogues (chemical castration) is used to reduce androgen levels, 90% of which are produced in the testes. However, 10% of androgens are synthesized in the adrenals and by tumor cells, which are not amenable to these treatments. This leak produces sufficient androgens to continue stimulating prostate cancer cell growth [44].

The inhibition of 17α-hydroxylase-17, 20-lyase (CYP17) is a more effective method to eradicate androgen secretion since CYP17 enzyme is required in androgen biosynthesis regardless of organs [45]. Abiraterone acetate is CYP17 inhibitor and functions as an androgen biosynthesis inhibitor in both pre- and postdocetaxel setting of mCRPC. Another CYP17 inhibitor is Ketoconazole, which is less potent and used as an alternative when abiraterone is not available [46]. In the COU-AA-301 phase III trial, overall survival in the abiraterone with prednisone arm was 14.8 months versus 10.9 months in the prednisone only arm; a 35.4% reduction in the risk of death. In addition, there have been reports on its efficacy in pain palliation and prevention of SREs [47, 48]. The median time to occurrence of first SRE was at 25 months with abiraterone and prednisone compared to 20.3 months in the prednisone only arm. In patients with clinically significant pain at baseline, Abiraterone and prednisone resulted in less pain in 157 of 349 (45.0%) of patients versus 47 of 163 (28.8%) of patients receiving monotherapy. Notably faster palliation was achieved with abiraterone and prednisone with a median time to palliation of 5.6 months versus 13.7 months in those who only received prednisone [48]. Adverse effects, such as elevated mineralocorticoid levels, cardiac disorders and liver-function test abnormalities, were common in the abiraterone acetate treated patients. On April 28, 2011, the FDA approved abiraterone acetate for use in combination with prednisone for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel based on improvement overall survival.

Enzalutamide

Enzalutamide is a second-generation oral androgen receptor (AR) signaling inhibitor or antagonist previously known as MDV300. It has been approved by the FDA in 2012 for the treat-

ment of progression mCRPC in the postdocetaxel setting. The phase III AFFIRM was an international double-blind placebo controlled trial in 1199 men from 166 sites with mCRPC who have failed prior docetaxel-containing chemotherapy regimens. The primary endpoint of the trial was overall survival. Secondary endpoints included radiographic progression-free survival, time to PSA progression, quality of life, and time until first skeletal-related event. An improvement in the primary endpoint was achieved with a median of 18.4 months in men who received enzalutamide versus 13.6 months in men received placebo. For the secondary endpoint, enzalutamide was also able to retard SREs with delayed first SRE time at 16.7 months while those who received placebo had first SRE time in 13.3 months in avaerage (hazard radio, 0.62; P<0.001). All parameters on pain palliation confirmed the more favorable response to enzalutamide compared to the placebo arm, including pain progression time, mean reduction in pain intensity and interference [49, 50]. This result demonstrated a favorable side effect profile of Enzalutamide indicating it is very well tolerated in patients.

Treatment strategy targets tyrosine or Src kinases

Cabozantinib

Cabozantinib (XL184) is a novel receptor tyrosine kinase inhibitor which inhibits the vascular endothelial growth factor receptor 2 (VEGFR2) and the hepatocyte growth factor c-Met. In a phase II trial of prostate cancer patients, 87% of whom had bone metastases, cabozantinib resulted in the partial resolution of bone lesions in 56% of patients and complete resolution in 19% [51]. In a dose-finding study, 40 mg cabozantinib was found to be associated with a high rater of bone scan response than 20 mg and with better tolerability than 60 mg [51]. Encouraging data from the phase II trials has led to the development of two phase III trials of cabozantinib in mCRPC, COMET-1 (NCT0160-5227) and COMET-2 (NCT01522443). First results of these two trials will not be available until mid-2014.

Src Family Kinase (SFK) inhibitors

The nonreceptor protein tyrosine kinase Src plays a pivotal role in the signal transduction pathways involved in both normal and malignant cell functions including proliferation, migration, and adhesion. SFKs are also essential for bone remodeling by stimulating osteoclasts and suppressing osteoblasts [52-56]. Several dual inhibitors of Src and Bcr-Abl tyrosine kinases, such as Dasatinib, Saracatinib and Bosutinib, have been studied in patients with prostate cancer.

Dasatinib is not only effective as a monotherapy in trials for CRPC patients, but may also function synergistically in combination with other chemotherapies [57-60]. The combination of Dasatinib and Docetaxel demonstrated a >50% reduction in PSA among 57% of patients and a partial disease response among 60% of patients. Urinary N-telopeptide of type I collagen (NTx) levels, an indicator of bone resorption, decreased in 87% of the patients with manageable toxicity [61]. A follow-up study demonstrated improvements in bone scans, high rates of soft tissue responses, and modulation of markers of bone turnover in 46 patients with mCRPC [58]. Phase II trials of Saracatinib (AZD-0530) have been carried out as a mono-therapy for patients with castrate resistant PCa (NCT00513071) in comparison with ZA on patients with metastatic PCa or breast cancer. The results are pending. Bosutinib (SKI-606) was shown to block PCa invasion, growth, and metastasis in preclinical studies [62].

The only Src-specific inhibitor, KX2-391 (Kinex Pharmaceuticals, NY, US), is a small molecule that binds to Src's peptide substrate-binding side. In a single-arm Phase II study in men with metastatic CRPC, twice daily use of 40 mg of KX2-391 did not show antitumor activity, even though modest effects on bone turnover markers were observed [63]. In summary, SFK inhibitors for inhibition of PCa bone metastasis are a promising class of agents, but more clinical studies are required to determine their optimal dosage and most effective combinations.

Conclusion

As summarized in the **Table 1**, in recent years, with better understanding of bone metastatic mechanisms, novel and more specific chemotherapeutic, immunologic, and radiopharmaceutical agents have demonstrated survival benefit and prevention SREs [47, 49, 64].

Table 1. List of the current and pending medications for CRPC

Name	Category	Main target	Status
Bisphosphonates	Compound	Bone environment: bone resorption	Approved
Denosumab	Humanized monoclonal antibody	Bone environment: bone resorption Directed against RANK-L	Approved
Alpharadin	α emitting Radiopharmaceutical	Sites of bone metastasis	Approved
Sipuleucel-T	Vaccine	T lymphocytes and helper $CD4^+$ lymphocytes	Approved
Abiraterone	Compound	androgen biosynthesis inhibitor inhibits 17α-hydroxylase-17, 20-lyase (CYP17)	Approved for use with prednisone
Enzalutamide (MDV300)	Compound	Androgen receptor (AR) signaling pathway	Approved
Cabozantinib	Compound	Receptor tyrosine kinases inhibitor Hepatocyte growth factor c-Met and VEGFR2	Phase III
Dasatinib	Compound	dual inhibitors to Src and Bcr-Abl tyrosine kinases	Phase II
Saracatinib	Compound	dual inhibitors to Src and Bcr-Abl tyrosine kinases	Phase II
Bosutinib	Compound	dual inhibitors to Src and Bcr-Abl tyrosine kinases	preclinical
KX2-391	Compound	Src-specific inhibitor	Phase II

Despite that the approved drugs still cannot prevent bone-metastasis prostate cancer progression, novel strategies have been proposed to further potentiate the antitumor effects of these agents or reduce their adverse effects and complications. Now with a lot of expanded treatment options available for treatment of mCRPC, making a tailored treatment for each patient to maximize the treatment efficacy in disease control may require better molecular characterization of the tumor cells. Further investigations on the selection criteria to determine those most likely to respond to a certain therapy are essential. Better understanding of the molecular mechanism at the individual patient level may aid clinicians in making the best choice among many therapeutic options for each patient. Further efforts are necessary to optimize the drug combination to prolong progression free and overall survival, as well as to improve and quality of life of affected patients.

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References

[1] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

[2] Ross RW and Kantoff PW. Hormone-refractory prostate cancer: choosing the appropriate treatment option. Oncology (Williston Park) 2007; 21: 185-193; discussion 194, 199-200.

[3] Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, Burch PA, Berry D, Moinpour C, Kohli M, Benson MC, Small EJ, Raghavan D and Crawford ED. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 351: 1513-1520.

[4] Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012; 62: 220-241.

[5] Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. Support Care Cancer 2008; 16: 879-889.

[6] El-Amm J, Freeman A, Patel N and Aragon-Ching JB. Bone-Targeted Therapies in Metastatic Castration-Resistant Prostate Cancer: Evolving Paradigms. Prostate Cancer 2013; 2013: 210686.

[7] Adler RA. Management of osteoporosis in men on androgen deprivation therapy. Maturitas 2011; 68: 143-147.

[8] Li X, Liao J, Park SI, Koh AJ, Sadler WD, Pienta KJ, Rosol TJ and McCauley LK. Drugs which in-

hibit osteoclast function suppress tumor growth through calcium reduction in bone. Bone 2011; 48: 1354-1361.

[9] Soki FN, Li X, Berry J, Koh A, Sinder BP, Qian X, Kozloff KM, Taichman RS and McCauley LK. The effects of zoledronic acid in the bone and vasculature support of hematopoietic stem cell niches. J Cell Biochem 2013; 114: 67-78.

[10] Rogers MJ, Watts DJ and Russell RG. Overview of bisphosphonates. Cancer 1997; 80: 1652-1660.

[11] Oades GM, Coxon J and Colston KW. The potential role of bisphosphonates in prostate cancer. Prostate Cancer Prostatic Dis 2002; 5: 264-272.

[12] 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.

[13] 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.

[14] Ernst DS, Tannock IF, Winquist EW, Venner PM, Reyno L, Moore MJ, Chi K, Ding K, Elliott C and Parulekar W. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. J Clin Oncol 2003; 21: 3335-3342.

[15] Small EJ, Smith MR, Seaman JJ, Petrone S and 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.

[16] Edwards BJ, Gounder M, McKoy JM, Boyd I, Farrugia M, Migliorati C, Marx R, Ruggiero S, Dimopoulos M, Raisch DW, Singhal S, Carson K, Obadina E, Trifilio S, West D, Mehta J and Bennett CL. Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. Lancet Oncol 2008; 9: 1166-1172.

[17] McCauley LK and Li X. Distinguishing features of the oral cavity and its predisposition to osteonecrosis. J Musculoskelet Neuronal Interact 2007; 7: 356-357.

[18] de Barros AL, Mota L, Soares DC, de Souza CM, Cassali GD, Oliveira MC and Cardoso VN. Long-circulating, pH-sensitive liposomes versus long-circulating, non-pH-sensitive liposomes as a delivery system for tumor identification. J Biomed Nanotechnol 2013; 9: 1636-1643.

[19] Liu CY, Xu JY, Shi XY, Huang W, Ruan TY, Xie P and Ding JL. M2-polarized tumor-associated macrophages promoted epithelial-mesenchymal transition in pancreatic cancer cells, partially through TLR4/IL-10 signaling pathway. Lab Invest 2013; 93: 844-854.

[20] Qian BZ and Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell 2010; 141: 39-51.

[21] Sturge J, Caley MP and Waxman J. Bone metastasis in prostate cancer: emerging therapeutic strategies. Nat Rev Clin Oncol 2011; 8: 357-368.

[22] Marra M, Salzano G, Leonetti C, Porru M, Franco R, Zappavigna S, Liguori G, Botti G, Chieffi P, Lamberti M, Vitale G, Abbruzzese A, La Rotonda MI, De Rosa G and Caraglia M. New self-assembly nanoparticles and stealth liposomes for the delivery of zoledronic acid: a comparative study. Biotechnol Adv 2012; 30: 302-309.

[23] Hiraoka K, Zenmyo M, Watari K, Iguchi H, Fotovati A, Kimura YN, Hosoi F, Shoda T, Nagata K, Osada H, Ono M and Kuwano M. Inhibition of bone and muscle metastases of lung cancer cells by a decrease in the number of monocytes/macrophages. Cancer Sci 2008; 99: 1595-1602.

[24] Kim SW, Kim JS, Papadopoulos J, Choi HJ, He J, Maya M, Langley RR, Fan D, Fidler IJ and Kim SJ. Consistent interactions between tumor cell IL-6 and macrophage TNF-alpha enhance the growth of human prostate cancer cells in the bone of nude mouse. Int Immunopharmacol 2011; 11: 862-872.

[25] Matsuzaki K, Udagawa N, Takahashi N, Yamaguchi K, Yasuda H, Shima N, Morinaga T, Toyama Y, Yabe Y, Higashio K and Suda T. Osteoclast differentiation factor (ODF) induces osteoclast-like cell formation in human peripheral blood mononuclear cell cultures. Biochem Biophys Res Commun 1998; 246: 199-204.

[26] Burgess TL, Qian Y, Kaufman S, Ring BD, Van G, Capparelli C, Kelley M, Hsu H, Boyle WJ, Dunstan CR, Hu S and Lacey DL. The ligand for osteoprotegerin (OPGL) directly activates mature osteoclasts. J Cell Biol 1999; 145: 527-538.

[27] Lacey DL, Tan HL, Lu J, Kaufman S, Van G, Qiu W, Rattan A, Scully S, Fletcher F, Juan T, Kelley M, Burgess TL, Boyle WJ and Polverino AJ. Osteoprotegerin ligand modulates murine osteoclast survival in vitro and in vivo. Am J Pathol 2000; 157: 435-448.

[28] O'Brien EA, Williams JH and Marshall MJ. Osteoprotegerin ligand regulates osteoclast adherence to the bone surface in mouse calvaria. Biochem Biophys Res Commun 2000; 274: 281-290.

[29] Fizazi K, Lipton A, Mariette X, Body JJ, Rahim Y, Gralow JR, Gao G, Wu L, Sohn W and 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.

[30] Smith MR, Saad F, Egerdie B, Szwedowski M, Tammela TL, Ke C, Leder BZ and Goessl C. Effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer. J Urol 2009; 182: 2670-2675.

[31] 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.

[32] Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R and 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.

[33] Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, Miller K, Sieber P, Karsh L, Damiao R, Tammela TL, Egerdie B, Van Poppel H, Chin J, Morote J, Gomez-Veiga F, Borkowski T, Ye Z, Kupic A, Dansey R and 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.

[34] Brady D, Parker CC and O'Sullivan JM. Bone-targeting radiopharmaceuticals including radium-223. Cancer J 2013; 19: 71-78.

[35] Goyal J and Antonarakis ES. Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases. Cancer Lett 2012; 323: 135-146.

[36] Nilsson S, Larsen RH, Fossa SD, Balteskard L, Borch KW, Westlin JE, Salberg G and Bruland OS. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. Clin Cancer Res 2005; 11: 4451-4459.

[37] Shore ND, Mantz CA, Dosoretz DE, Fernandez E, Myslicki FA, McCoy C, Finkelstein SE and Fishman MN. Building on sipuleucel-T for immunologic treatment of castration-resistant prostate cancer. Cancer Control 2013; 20: 7-16.

[38] Paller CJ and Antonarakis ES. Sipuleucel-T for the treatment of metastatic prostate cancer: promise and challenges. Hum Vaccin Immunother 2012; 8: 509-519.

[39] Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363: 411-422.

[40] Higano CS, Schellhammer PF, Small EJ, Burch PA, Nemunaitis J, Yuh L, Provost N and Frohlich MW. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer 2009; 115: 3670-3679.

[41] Small EJ, Schellhammer PF, Higano CS, Redfern CH, Nemunaitis JJ, Valone FH, Verjee SS, Jones LA and Hershberg RM. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006; 24: 3089-3094.

[42] Anassi E and Ndefo UA. Sipuleucel-T (provenge) injection: the first immunotherapy agent (vaccine) for hormone-refractory prostate cancer. P T 2011; 36: 197-202.

[43] Geller J. Basis for hormonal management of advanced prostate cancer. Cancer 1993; 71: 1039-1045.

[44] Titus MA, Schell MJ, Lih FB, Tomer KB and Mohler JL. Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer. Clin Cancer Res 2005; 11: 4653-4657.

[45] Yin L, Hu Q and Hartmann RW. Recent progress in pharmaceutical therapies for castration-resistant prostate cancer. Int J Mol Sci 2013; 14: 13958-13978.

[46] Peer A, Gottfried M, Sinibaldi V, Carducci MA, Eisenberger MA, Sella A, Leibowitz-Amit R, Berger R and Keizman D. Comparison of abiraterone acetate versus ketoconazole in patients with metastatic castration resistant prostate cancer refractory to docetaxel. Prostate 2013; [Epub ahead of print].

[47] de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Flechon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI; COU-AA-301 Investigators. Abiraterone and increased survival in meta-

static prostate cancer. N Engl J Med 2011; 364: 1995-2005.

[48] Logothetis CJ, Basch E, Molina A, Fizazi K, North SA, Chi KN, Jones RJ, Goodman OB, Mainwaring PN, Sternberg CN, Efstathiou E, Gagnon DD, Rothman M, Hao Y, Liu CS, Kheoh TS, Haqq CM, Scher HI and de Bono JS. 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 2012; 13: 1210-1217.

[49] Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187-1197.

[50] Hoffman-Censits J and Kelly WK. Enzalutamide: a novel antiandrogen for patients with castrate-resistant prostate cancer. Clin Cancer Res 2013; 19: 1335-1339.

[51] Lee RJ, Saylor PJ, Michaelson MD, Rothenberg SM, Smas ME, Miyamoto DT, Gurski CA, Xie W, Maheswaran S, Haber DA, Goldin JG and Smith MR. A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases. Clin Cancer Res 2013; 19: 3088-3094.

[52] Wu Z, Chang PC, Yang JC, Chu CY, Wang LY, Chen NT, Ma AH, Desai SJ, Lo SH, Evans CP, Lam KS and Kung HJ. Autophagy Blockade Sensitizes Prostate Cancer Cells towards Src Family Kinase Inhibitors. Genes Cancer 2010; 1: 40-49.

[53] Boyce B and Xing L. Src inhibitors in the treatment of metastatic bone disease: rationale and clinical data. Clin Investig (Lond) 2011; 1: 1695-1706.

[54] Edwards J. Src kinase inhibitors: an emerging therapeutic treatment option for prostate cancer. Expert Opin Investig Drugs 2010; 19: 605-614.

[55] Saad F and Lipton A. SRC kinase inhibition: targeting bone metastases and tumor growth in prostate and breast cancer. Cancer Treat Rev 2010; 36: 177-184.

[56] Araujo JC, Poblenz A, Corn P, Parikh NU, Starbuck MW, Thompson JT, Lee F, Logothetis CJ and Darnay BG. Dasatinib inhibits both osteoclast activation and prostate cancer PC-3-cell-induced osteoclast formation. Cancer Biol Ther 2009; 8: 2153-2159.

[57] Twardowski PW, Beumer JH, Chen CS, Kraft AS, Chatta GS, Mitsuhashi M, Ye W, Christner SM and Lilly MB. A phase II trial of dasatinib in patients with metastatic castration-resistant prostate cancer treated previously with chemotherapy. Anticancer Drugs 2013; 24: 743-753.

[58] Araujo JC, Trudel GC and Paliwal P. Long-term use of dasatinib in patients with metastatic castration-resistant prostate cancer after receiving the combination of dasatinib and docetaxel. Cancer Manag Res 2013; 6: 25-30.

[59] Yu EY, Massard C, Gross ME, Carducci MA, Culine S, Hudes G, Posadas EM, Sternberg CN, Wilding G, Trudel GC, Paliwal P and Fizazi K. Once-daily dasatinib: expansion of phase II study evaluating safety and efficacy of dasatinib in patients with metastatic castration-resistant prostate cancer. Urology 2011; 77: 1166-1171.

[60] Yu EY, Wilding G, Posadas E, Gross M, Culine S, Massard C, Morris MJ, Hudes G, Calabro F, Cheng S, Trudel GC, Paliwal P and Sternberg CN. Phase II study of dasatinib in patients with metastatic castration-resistant prostate cancer. Clin Cancer Res 2009; 15: 7421-7428.

[61] Araujo JC, Mathew P, Armstrong AJ, Braud EL, Posadas E, Lonberg M, Gallick GE, Trudel GC, Paliwal P, Agrawal S and Logothetis CJ. Dasatinib combined with docetaxel for castration-resistant prostate cancer: results from a phase 1-2 study. Cancer 2012; 118: 63-71.

[62] Rabbani SA, Valentino ML, Arakelian A, Ali S and Boschelli F. SKI-606 (Bosutinib) blocks prostate cancer invasion, growth, and metastasis in vitro and in vivo through regulation of genes involved in cancer growth and skeletal metastasis. Mol Cancer Ther 2010; 9: 1147-1157.

[63] Antonarakis ES, Heath EI, Posadas EM, Yu EY, Harrison MR, Bruce JY, Cho SY, Wilding GE, Fetterly GJ, Hangauer DG, Kwan MF, Dyster LM and Carducci MA. A phase 2 study of KX2-391, an oral inhibitor of Src kinase and tubulin polymerization, in men with bone-metastatic castration-resistant prostate cancer. Cancer Chemother Pharmacol 2013; 71: 883-892.

[64] Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, Staffurth JN, North S, Vogelzang NJ, Saad F, Mainwaring P, Harland S, Goodman OB Jr, Sternberg CN, Li JH, Kheoh T, Haqq CM, de Bono JS; COU-AA-301 Investigators. 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 2012; 13: 983-992.