Therapeutic opportunities for castration-resistant prostate cancer patients with bone metastases

Fable Zustovich a,*, Francesca Fabiani b

a Oncologia Medica 1-Istituto Oncologico Veneto – IRCCS, Padova, Italy
b Department of Emergency-Urgency, San Giuseppe General Hospital, Empoli (Florence), Italy

Accepted 10 January 2014

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Abstract

Patients with castration-resistant prostate cancer are burdened not only with an unavoidable risk of mortality but also by severe mobility issues. This disease has a high tendency to induce bone metastases with concomitant general suffering, impaired mobility, and reduced self-sufficiency. The treatment of bone pain consists of opioids, nonsteroidal anti-inflammatory drugs, radiopharmaceuticals, and radiotherapy. To date, abiraterone, enzalutamide, zoledronate and denosumab are the only drugs able to delay skeletal events, and docetaxel is the only chemotherapeutic agent able to prolong survival after castration progression. Recently, 5 new drugs have proven to be efficacious in prolonging survival. Sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium-223 have broadened the therapeutic choices, thus changing the

Keywords: Castration-resistant prostate cancer; Enzalutamide; Abiraterone; Radium-223; Cabazitaxel; Docetaxel; Bone metastases

* Corresponding author. Tel.: +39 3479775504; fax: +39 498215904.
E-mail address: fable.zustovich@iveneto.it (F. Zustovich).

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http://dx.doi.org/10.1016/j.critrevonc.2014.01.003

Please cite this article in press as: Zustovich F, Fabiani F. Therapeutic opportunities for castration-resistant prostate cancer patients with bone metastases. Crit Rev Oncol/Hematol (2014), http://dx.doi.org/10.1016/j.critrevonc.2014.01.003
1. Introduction

The incidence of prostate cancer in Western countries accounts for an estimated 900,000 new cases per year, and this figure is expected to increase due to improvements in health education, the widening scope of screening campaigns, and longer life spans [1,2]. Even though the localized forms of this disease for the most part appear curable or fairly manageable and associated mortality is relatively low compared with other tumors, prostate cancer represents the second cause of mortality in men. Epidemiological investigations reported that in 2007 more than 28,000 related deaths were recorded in the United States [2].

For more than 70 years, surgery, radiotherapy, or pharmacologic therapies aimed at reducing levels of testosterone and its metabolites (androgen deprivation) have been the cornerstone for the treatment of this disease. In a relatively large number of cases, androgen deprivation, most often accomplished with luteinizing hormone-releasing hormone agonists with or without antiandrogen therapies, maintains tumor-control growth generally lasting a consistent length of time. After that, patients develop signs of progression independent of the maintenance of hormone blockade [3,4]. Such a condition, described as castration-resistant prostate cancer (CRPC) [4], results in a highly debilitating disease due to the high tendency of the tumor to induce bone metastases that dramatically increase the risk of pathologic fractures and skeletal complications including nervous tissue compressions and hypercalcemia [5].

These complications, together called skeletal-related events (SREs), are associated with impaired mobility, general suffering, reduced self-sufficiency, reduced quality of life, increased mortality, and increased health care costs [6–8]. Although only 3% of patients at initial diagnosis display bone involvement, this percentage rises to 90% in patients with metastatic CRPC (mCRPC) [8–10]. In contrast, visceral metastases (lung, liver, adrenal gland, and kidney) are estimated at approximately 25% and generally indicate an aggressive disease [11–13]. According to a recent paper, the incidence of visceral metastases have been increasing in the recent years, due to a more common detection and to the introduction of treatments increasing survival [12]. With the goal of extending survival as much as possible in these patients, positive results were initially obtained with chemotherapy. Docetaxel combined with prednisone was shown to delay tumor progression in patients with mCRPC achieving a survival of about 19 months [11]. Subsequently, phase 3 investigations with newer agents identified 5 agents: abiraterone, cabazitaxel, sipuleucel-T, enzalutamide, and radium-223. Although acting on different targets, all these drugs were able to further extend survival in both chemo-naïve patients and those previously treated with docetaxel [14].

This review describes the therapies presently available for patients with CRPC and bone metastases. After reviewing international recommendations and phase 3 results, we focused on the agents currently helpful to improve overall survival (OS), reduce pain, and delay time to SREs.

2. Bone metastases in patients with metastatic castration-resistant prostate cancer

Among all human tumors, prostate cancer, because of its peculiarly strong cell avidity for bone tissue, displays a high risk of bony metastases. Such avidity is higher compared with breast and lung tumors that represent the second and third cancers characterized by bone dissemination [15,16], evidence substantiated by statistical and postmortem analyses, and by clinical studies [11,13,17,18].

Like breast cancer, the first site of the spread of prostate cancer is the spine followed by the pelvis, hip, femur, and skull [8]. In contrast to other human tumors, bone metastases along with their related complications represent the leading cause of death for mCRPC patients [19]. Some authors report that about 50% of patients with bone metastases die within 30–35 months from diagnosis [20–22]. Overall, it is believed that the dimension of bone metastases, the intensity of pain, and the presence of SREs indicate a shorter survival. Data report that for patients with bone metastases, the risk of death is 6.6 times greater than that of nonmetastatic patients, and this risk increases 10.2 times in patients whose bone metastases are associated with SREs [23]. Some authors consider the time to the onset of SREs as a prognostic factor for survival in patients with mCRPC [23,24]. Further important survival predictors are the volume of bone metastases and the intensity of the pain [25].

Although lytic bone lesions have been documented, the skeletal metastases from prostate cancer are predominantly “bone forming,” defined as osteoblastic lesions. Studies demonstrated that the metastatic cells stimulate osteoblast proliferation to release specific growth factors causing an increased deposition in bone matrix and in the bone microenvironment (Fig. 1) [7,8].

Radiologic imaging of bone lesions shows an irregular shape and an imbalanced number of bone trabeculae without histologic evidence of an increase of the number of osteoclasts [13,26]. The level of markers of bone resorption in patients with bone metastases is greater than nonmetastatic
patients [27]. Some authors claim that the serum level of bone-specific alkaline phosphatase (ALP) could be the best strategy to monitor bone metastases in mCRPC patients rather than a simple prostate-specific antigen (PSA) evaluation [28]. This seemed to be confirmed in a recent phase 3 trial undertaken in patients stratified according to ALP baseline levels where the time to achieve an increase of 25% or more of ALP was evaluated as a secondary end point for the drug evaluation [29].

This predominant osteoblastic activity induces alterations of normal bone homeostasis on the basis of bone reabsorption (osteoclastic activity) and bone storage (osteoblast activity), eventually resulting in the weakening of skeletal tissue [30]. Such alterations give rise to an increase of pain and SREs, particularly pathologic fractures and compression of the spinal cord, requiring orthopedic surgery, neurosurgery, palliative radiotherapy for bone pain, and sometimes changes in cancer therapy [30].

Bone metastases can also worsen the framework of bone fragility already determined by other factors. In addition to the presence of the tumor, which intrinsically represents a risk factor for osteoporosis [31], the loss of bone tissue due to the androgen deprivation induced by therapies must be considered [32]. Some authors estimate that 90% of patients with prostate cancer have an inadequate calcium intake [33].

Fortunately, opportunities to improve the management of mCRPC patients with bone metastases have increased. As reported in Table 1, in addition to the traditional palliative agents for the management of pain such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, external-beam radiation therapy (EBRT) and radiopharmaceuticals, new recent systemic approaches able to delay the onset of SREs, relieve pain, and prolong survival have been introduced [30].

3. Agents effective only for pain management

Certain agents demonstrate efficacy in pain palliation, without any significant impact on delaying time to the first SRE and/or prolonging OS. The conventional symptomatic treatment of metastatic bone pain requires multidisciplinary therapeutic approaches such as EBRT localized at the painful area at risk of fracture and drugs containing radioactive materials (radiopharmaceuticals) in combination with analgesic therapy (opioids or NSAIDs).

3.1. Therapy with nonsteroidal anti-inflammatory drugs alone or in combination with opioids

NSAIDs, associated with paracetamol, represent the first-choice treatment of mild intensity cancer pain. The combination of these agents with minor opioids (codeine and tramadol) or major opioids (morphine, methadone, and fentanyl) represents the treatment of choice for moderate and severe cancer pain, respectively. In contrast to opioids, NSAIDs have a ceiling effect, so no therapeutic advantage is gained by increasing the doses above the standard recommendations [34].

A review of the Cochrane databases concerning the use of NSAIDs for cancer pain palliation evaluated 42 randomized trials in which NSAIDs were used alone or in combination with opioids. The study demonstrated the increased effectiveness of NSAIDs compared with placebo, but no NSAID showed superior results [35]. Some authors support the treatment with selective inhibitors of cyclo-oxgenase-2 because they may provide benefits not only for analgesia, but also for the presumed anticancer effect [36].

Present recommendations of the World Health Organization (WHO) concerning the use of drugs for cancer pain relief suggest an approach based on 3 basic levels of pain according
to the severity of symptoms. This approach includes the use of NSAIDs alone for mild pain, and their combination with minor opioids or major opioids for moderate and severe pain, respectively [34] (Fig. 2).

### 3.2. External-beam radiation therapy

EBRT is a cost-effective therapy for bone pain, specifically suitable for localized disease. Retrospective analyses document pain relief in 80% of patients, and complete responses are achieved in a third of them. Despite the good results obtained in palliation after a single administration, retreatment is required in about 25% of patients [37]. Due to the presence of multiple bone metastases, a possible therapeutic option is hemi-body therapy.

Because of the low selectivity of radiotherapy, this procedure may also convey radiation to healthy cells, and consequently, there is the risk of bone marrow and gastrointestinal toxicities [38].

### 3.3. Radiopharmaceuticals

The possibility to achieve pain relief from bony metastases has been demonstrated in phase 3 studies with strontium-89 (Sr 89) and samarium-153 (Sm 153-EDTMP3), 2 bone-targeting β-emitting radiopharmaceuticals [39,40]. Both drugs are commercially available and approved by the US Food and Drug Administration (FDA) for the palliation of pain due to skeletal metastases [41,42].

As previously mentioned, the use of radiopharmaceuticals is generally restricted to patients with multifocal bone disease who cannot be treated with EBRT.

The mechanism of action of Sr 89 and Sm 153-EDTMP3 is commonly called bone seeking because the 2 β-radioisotopes, showing a chemical structure very similar to calcium, are able to be incorporated into the bone and reach the metastatic sites characterized by extremely intense osteoblastic activity [43]. The radioactivity of these 2 β-radioisotopes, both associated with a penetration energy up to 2.4 mm in bone tissues, is able to induce single-strand DNA damage and subsequently the death of cancer cells. This therapy attains a symptomatic benefit in the 55–80% of patients with duration of responses ranging between 2 and 17 weeks [40,44].

An interesting meta-analysis reported that β-emitting radioisotopes supply benefit with reduction of pain (1–6 months) without increasing analgesic consumption [45].

The β-radioisotropharmaceuticals are generally burdened by adverse effects on the bone marrow such as transient myelosuppression mainly consisting of leukopenia and thrombocytopenia [46]. Despite the effectiveness in bony metastasis pain relief and the possibility of reducing consumption of analgesics and improving quality of life, β-radioisotropharmaceuticals did not prove to be effective in extending survival [46].

### 4. Treatment to delay or prevent skeletal-related events and relieve bone pain

Bisphosphonates and denosumab are effective agents to prevent and delay SREs and for pain palliation. However, similar to other bone-targeting agents such as β-radioisotropharmaceuticals, the 2 drugs did not demonstrate the ability to extend OS.

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4.1. Bisphosphonates

Bisphosphonates, considered the first bone-target agents, show a chemical structure similar to the normal component of bone matrix pyrophosphate. Therefore they are easily absorbed by, and bind to, the hydroxyapatite crystals causing the inhibition of bone reabsorption by osteoclasts [47].

Many studies have shown that the use of bisphosphonates in nonmetastatic prostate cancer reduces the bony loss related to androgen-deprivation therapy. Except for zoledronic acid, no other bisphosphonate definitively demonstrated statistically significant efficacy and long-term clinical benefit by preventing SREs [48, 49].

In a phase 3 trial, the administration of zoledronic acid (4 mg given as a 15-min infusion every 3 weeks) vs placebo in 643 mCRPC patients resulted in a reduction of the rate of patients having at least 1 SRE (33% vs 44%; \(P = 0.021\)). It also displayed consistent efficacy across all secondary end points (time to the first SRE, skeletal morbidity rate, proportion of patients with individual SRE events, time to disease progression, objective bone lesion response, bone biochemical markers, and quality of life) and improvements of pain and analgesia scores [50]. The study led to the approval of zoledronic acid by the US and European regulatory authorities for the prevention of SREs in patients with prostate, breast, and lung cancer.

A well-known adverse event related to zoledronic acid is nephrotoxicity. The risk of impaired renal function can be circumvented by monitoring creatinine clearance and avoiding rapid infusions. Other adverse events requiring attention include hypocalcemia and osteonecrosis of the jaw (ONJ) [51]. Because the risk of ONJ increases with trauma and infections, it is recommended an assessment of the dental status of patients before administration of bisphosphonate therapy [51]. In case of patients receiving bisphosphonate it is recommended to avoid invasive dental, recommending a good oral hygiene [51].

4.2. Denosumab

Denosumab is a monoclonal antibody directed against the receptor activator of nuclear factor-κB ligand that can trigger the activity of osteoclasts. The drug binds the surface of osteoclastic cells preventing them from tying up the receptor, thus decreasing bone reabsorption and increasing bone mass [52].

The first phase 3 study undertaken in patients undergoing androgen-deprivation therapy demonstrated the ability of denosumab (60 mg every 6 months) to avoid bone tissue density depletion and then to reduce the incidence of new spine fractures compared with placebo. The study did not demonstrate any significant benefit of OS following denosumab therapy [53].

A second phase 3 study, carried out with 1904 patients with mCRPC, compared denosumab (120 mg administered subcutaneously every 4 weeks) with zoledronic acid (4 mg intravenously given every 3 weeks) [54]. The primary end point, consisting of the evaluation of the delay of time to first SRE, showed significant benefit for the group of patients treated with denosumab (20.7 months vs 17.1 months; hazard ratio [HR]: 0.82; \(P < 0.001\) for noninferiority, \(P = 0.008\) for superiority). OS, disease progression, and rates of adverse events and serious adverse events were similar in the 2 groups [54].

Contrary to all expectations, in comparison with zoledronic acid the study did not reveal a greater reduction for denosumab regarding back pain and at the wide ends of long bones [54]. Higher levels of hypocalcemia were observed in patients treated with denosumab as compared with those treated with the comparator (13% vs 6%; \(P < 0.001\)). However, in contrast to zoledronic acid, denosumab can also be used in patients with impaired renal function (creatinine clearance < 30 mL per minute) [54]. Similar to zoledronic acid, denosumab therapy was also associated with ONJ [54]. The main differences between zoledronic acid and denosumab are summarized in Table 2.

The FDA approved denosumab (120 mg every 4 weeks) for the prevention of SREs in patients with bone metastases. The drug was also approved at a different dosage (60 mg every 6 months) to increase bone mass in CRPC patients undergoing androgen deprivation [54].

5. Agents showing prolongation of survival

5.1. Docetaxel

Since 2004, docetaxel has been approved by the European and American health authorities for patients progressing following androgen deprivation. Docetaxel represents the only standard first-line chemotherapy for mCRPC, and the role of the drug was established after 2 randomized phase 3 studies undertaken in patients with symptomatic or rapidly progressing disease.

The first study (TAX 327) compared docetaxel (every 3 weeks or weekly) plus prednisone vs mitoxantrone plus prednisone in a population of 1006 men [11]. In this study, 335 patients receiving docetaxel every 3 weeks showed higher

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Table 2
Main differences between zoledronic acid and denosumab.

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<tr>
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<td>20.7 months</td>
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<tr>
<td>Serious AE(^{a})</td>
<td>60%</td>
<td>63%</td>
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<tr>
<td>CTCAE grade 3–4 AE(^{a})</td>
<td>66%</td>
<td>72%</td>
</tr>
<tr>
<td>Calcium decrease grade</td>
<td>1%</td>
<td>5%</td>
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<tr>
<td>ONJ (all the grades)(^b)</td>
<td>77%</td>
<td>83%</td>
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<tr>
<td>Cost 4 weeks of therapy(^b)</td>
<td>953$</td>
<td>1672$</td>
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AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events (v3.0); ONJ, osteonecrosis of the jaw.
\(^{a}\) Fizazi Lancet (2011); 377:813–22.
\(^{b}\) Koo Support Care Cancer (2013) 21:1785–1791SRE – Median time to first on-study skeletal-related event.

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median OS (18.9 months vs 16.5 months; \(P=0.009\)) and higher rates of PSA response (i.e., 50% PSA reduction from baseline; 45% vs 32%, \(P<0.001\)) compared with the reference arm with mitoxantrone. This survival benefit was maintained during the long follow-up. The same schedule achieved the best pain palliation (35% vs 31% for the weekly schedule evaluated with the present pain intensity [PPI] scale), with a significant benefit in pain response compared with the combination of mitoxantrone and prednisone (35% vs 22%; \(P=0.01\)) [55].

The second study (SWOG 9916) also showed improvement of survival in patients treated with docetaxel (every 3 weeks) in combination with estramustine vs mitoxantrone plus prednisone [56]. Bone marrow toxicity was the principal serious adverse event [11,56]. To the best of our knowledge, no sound data concerning the impact of docetaxel on SREs or on bone metastases reduction have been reported.

5.2. Sipuleucel-T

Sipuleucel-T is the only therapeutic cancer vaccine currently approved in oncology. The drug is an autologous dendritic cell-based therapy, programmed to stimulate T cells against the antigen expressed by tumor cells of prostatic acid phosphatase (PAP). In sipuleucel-T, the PAP antigen, which is generally located in prostate cancer tissue, is linked to granulocyte–macrophage colony-stimulating factor acting as an immune cell activator [57].

A phase 3 study was conducted on 512 asymptomatic or minimally symptomatic mCRPC patients (IMPACT study) treated with the vaccine (administered according to the schedule of 3 repeated injections every 2 weeks) or placebo [57]. The study excluded patients with visceral metastases and patients with pathologic long-bone fractures, spinal cord compression, or with bone pain due to cancer.

The active arm was associated with a greater survival benefit of 4.1 months compared with placebo (25.8 vs 21.7), showing a 22% reduction of death risk (HR: 0.78). In this study, sipuleucel-T did not induce tumor regression, relief of symptoms, or delay disease progression. Bone pain results were similar in both arms of treatment (about 11%). The levels of incidence of bone fractures and the time to the first SRE were not reported in the study. Adverse events were generally moderate and transitory, mostly chills (54.1%), pyrexia (29.3%), and headache (16.0%) [57].

Sipuleucel-T received FDA approval in 2010 for the treatment of patients with asymptomatic or slightly symptomatic mCRPC regardless of the previous treatment line. The indication includes only patients with mCRPC with minimal or no symptoms, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. The therapy is not indicated for patients with liver metastases or less than 6 months of life expectancy. A considerable limitation for the current use of sipuleucel-T could be related to the lack of advantages in PFS observed in the pivotal study, this could have consequences on the clinical practice because physicians does not have any confirm of the real activity of the drug during the routinely follow-up. In addition, due to the cost and because it is not easy to predict who will really benefit from this vaccine, the use of sipuleucel-T outside the United States is extremely limited [58].

5.3. Cabazitaxel

Cabazitaxel is a semisynthetic taxane administered intravenously, designed to overcome the resistance frequently observed following treatment with docetaxel and paclitaxel [59]. Compared with previous generation taxanes, the molecule shows a lower affinity for the taxane efflux pump, thus offering greater penetration into the blood–brain barrier. Studies in vitro and in vivo clearly show the ability of this molecule to kill tumor-resistant cells to docetaxel [59,60].

The open-label phase 3 study (TROPIC study) enrolled mCRPC patients relapsed after first-line treatment with docetaxel. A total of 775 patients displaying 25% visceral and 84% bone metastases at baseline were randomized to treatment either with cabazitaxel (25 mg/m² 3 weekly) plus prednisone (10 mg once daily) or to mitoxantrone (12 mg/m² 3 weekly) plus prednisone (10 mg once daily) [61].

The study demonstrated a statistically significant benefit in terms of OS in patients treated with cabazitaxel (15.1 months vs 12.7 months; \(P<0.0001\)) with a 30% reduction of the risk of death (HR: 0.70).

The benefit in OS was observed even in patients with pain at baseline (HR: 0.76; 95% confidence interval [CI], 0.59–0.98).

However, in the TROPIC study, cabazitaxel showed only a slight reduction of grade 3 or higher pain compared with the control arm (1% vs 2%), and the full analysis of number and time to first SRE is not presently available. No improvement in pain relief was observed between the 2 arms (9.2% for cabazitaxel plus prednisone vs 7.7% for mitoxantrone plus prednisone evaluated according to the PPI scale; \(P=0.63\)).

Regarding adverse events, in the TROPIC study the incidence of grade 3 or higher neutropenia was 82% in patients treated with cabazitaxel compared with 58% in those treated with mitoxantrone; 7 deaths (2% of all deaths) for septic neutropenia were recorded in the cabazitaxel arm [61]. On the basis of this study, the US and European regulatory agencies in 2011 approved the use of cabazitaxel for patients with mCRPC after failure with docetaxel.

Activity and safety data of the drug were also examined in an expanded access program study. Although not published, an interim report presented at international meetings confirmed that the major toxicities of the drug are mainly related to neutropenia and diarrhea [62].

5.4. Abiraterone

Abiraterone acetate is the commercially available prodrug form of abiraterone, a progesterin derivative that binds and irreversibly inhibits the enzyme 17a-hydroxylase/C17.20-lyase
(CYP17A1), thus hampering androgen synthesis in adrenal glands, testicles, and prostate cancer, the only organs or tissues where this enzyme is expressed [63,64].

The administration of abiraterone is oral and requires a fasting state. The drug needs the concomitant administration of prednisone to prevent the toxicity derived from the excess of mineralocorticoids associated with the CYP17 blockade.

The efficacy and tolerability of abiraterone in patients with prostate cancer were demonstrated in 2 phase 3 studies undertaken in different lines of treatment. The first study compared abiraterone (1000 mg per day) combined with prednisone (5 mg twice daily) with prednisone (5 mg twice daily) plus placebo in 1195 patients with mCRPC who had relapsed after 1 or 2 lines of docetaxel-based chemotherapy (COU-AA-301 study) [65]. In this study, 90% of patients displayed bone metastases, 10% liver metastases, and 45% lymph node metastases. The primary end point, consisting of the evaluation of OS, was superior for the experimental arm (14.8 months vs 10.9 months) with a 35% risk reduction of death compared with the control arm. Similarly, all the secondary end points (PSA response, radiologic progression-free survival [PFS], and time to progression) were statistically superior in favor of the experimental arm.

Abiraterone resulted in actively reducing pain. In this study, pain response evaluated with the Brief Pain Inventory Scale accounted for 44% in the experimental arm and 27% in the control arm. The subgroup analysis revealed that the drug also showed a trend of efficacy in the subgroup of patients with visceral metastases. The adverse event profile was similar in the 2 arms, and in some cases the control arm showed a higher incidence of adverse events (nausea, vomiting, and back pain) [65].

A subsequent publication reported in detail the SRE events prospectively analyzed in the 2 arms of the study. The time to first SRE and the time to palliation of pain in particular were analyzed [66]. The study showed that the proportion of patients with SRE was similar in both treatment groups, but the median time to the first SRE was significantly delayed in patients treated with abiraterone plus prednisone (9.9 months vs 4.9 months).

The analysis of parameters revealing pain showed that the association of abiraterone combined with prednisone induced palliation of pain significantly superior and faster compared with the placebo plus prednisone arm. In addition, the evaluation of the subgroups of patients who were asymptomatic at baseline revealed that in the experimental arm the use of analgesics was reduced [66].

Based on this study, the FDA approved abiraterone in combination with low-dose prednisone for the treatment of patients with mCRPC who had received prior chemotherapy containing docetaxel.

A second study compared the 2 associated regimens of abiraterone (1000 mg/d) plus prednisone (5 mg twice daily) vs prednisone (5 mg twice daily) plus placebo in 1088 chemotherapy-naive CRPC patients (COU-AA-302 study) [67]. Patients enrolled in this trial generally presented with a good prognosis. The presence of visceral metastases was a criterion for exclusion; in addition, only asymptomatic patients or those with mild symptoms were enrolled. It appeared by observation that many patients at baseline were not taking narcotics for pain.

The study showed the ability to prolong time to progression and survival in the experimental arm, but, to date, no data are available about the possibility of delaying SRE. Concerning pain palliation, the association of abiraterone with prednisone was able to delay the time to administration of opioids. Bone pain was reported as an adverse event with approximately the same frequency in both arms [67]. Adverse events observed in the experimental arm were mild or moderate, predominantly consisting of fatigue, back or joint discomfort, peripheral edema, and gastrointestinal symptoms. This second study supported a new indication, and in December 2012 the FDA approved abiraterone for the treatment of mCRPC patients before a docetaxel-based regimen.

5.5. Enzalutamide

Enzalutamide, an antiandrogen drug, acts on multiple sites. The drug competes with androgen receptors with higher affinity compared with other antiandrogens. It blocks the nuclear translocation of androgen receptors and inhibits binding to chromosomal DNA, leading to cell apoptosis. In contrast to abiraterone, the administration of enzalutamide does not require the concomitant administration of steroids and a fasting state [68].

Enzalutamide (160 mg per day) was evaluated vs placebo in a phase 3 study conducted in 1199 patients with mCRPC previously treated with 1 or 2 chemotherapy regimens at least one of which contained a docetaxel regimen (AFFIRM study) [69]. About 43% of patients of the study received bisphosphonates. During the first phase of the study, seizures were observed in 5 patients treated with enzalutamide. As a precautionary measure the study was amended, forbidding the contemporary administration of substances lowering the seizure threshold.

The investigation achieved the primary end point set of superiority of OS over placebo (18.4 months vs 13.6 months). The superiority of enzalutamide was also observed in the secondary end points consisting of time to PSA progression, radiologic PFS, and time to first SRE. The former documented a delay of 16.7 months for patients with enzalutamide compared with 13.3 months for patients treated with placebo (95% CI, 14.6–19.1; 9.9 not yet reached; HR: 0.69; P < 0.001). Worthy of mention is that the drug turned out to be effective independent of the number of bone lesions (>20 or not).

Overall, adverse grade 3–4 events (including cardiotoxicity) were lower in patients treated with enzalutamide compared with those treated with placebo (45.3% vs 53.1%). Diarrhea, fatigue, and hot flushes were the more frequent adverse events. Musculoskeletal pain was 14% (1% was
grade 3 or higher) in patients with enzalutamide and 10% for patients receiving placebo (≥1% grade 3 or higher). Based on the AFFIRM study, enzalutamide was approved by US and European regulatory agencies in the second half of 2012.

A phase 3 trial comparing enzalutamide vs placebo in chemotherapy-naive patients is presently ongoing (PREVAIL study) [70].

5.6. Radium-223

Radium-223 in the form of radium dichloride is a calcium-mimetic, bone-seeking radiopharmaceutical drug. In contrast to the β-emitting Sr 89 and Sm 153-EDTMP, radium-223 is a radionuclide emitting predominantly α particles, which, compared with low linear energy transfer radiations as β particles and γ rays, are characterized by short range (<0.1 mm) and highly energetic radiation able to induce double-strand DNA breaks [71–73] (Table 3). Therefore, α particles are classified as high-linear energy transfer radiation, which is generally more lethal to cells. An additional important difference characterizing β and γ emitters is that, due to the relatively long range of the radiation, the exposure of surrounding tissues can be associated with toxicities. In opposition, these toxicities are reduced in case of exposure to α radiation because of the shorter radiation range (<100 μm; e.g., 2–10 cell diameters) and lower surrounding tissue penetration. The hematologic toxicity is prevented by the first cell layer that can stop radionuclide penetration in the bone marrow [74]. At the present time, radium-223 is the only bone-seeking drug demonstrated to extend OS in mCRPC patients, thus confirming the key role of targeting bone metastases to improve patient prognosis.

The phase 3 trial enrolled 922 symptomatic patients with only bone metastases due to CRPC; among them, 60% were failing and 40% were not eligible or refused a prior docetaxel-based chemotherapy (ALSYMPCA study). Patients enrolled in the study were given up to 6 intravenous treatments of radium-223 at 50 kBq/kg or placebo, with an interval of 4 weeks between each treatment. The primary end point was OS, and the secondary end points included time to first SRE, time to total serum bone-specific ALP progression, total ALP response and normalization, time to PSA progression, safety, and quality of life. Patients were stratified according to ALP level, use of bisphosphonates, previous docetaxel-containing chemotherapy, and baseline ECOG PS

Compared with placebo, radium-223 significantly improved OS in patients with CRPC with bone metastases (2-sided P = 0.00007; HR: 0.658; 95% CI, 0.581–0.832; median OS 14.9 months vs 11.3 months, respectively). A similar trend in favor of survival was seen in different subgroups of patients according to the use of bisphosphonates, previous treatment with docetaxel, and PS (except for ECOG PS ≥ 2 that did not reach statistical significance).

A beneficial effect was also observed regarding all the secondary end points. In particular, the time to first SRE was significantly prolonged (median: 15.6 months vs 9.8 months, respectively; HR: 0.658; 95% CI, 0.522–0.830; P = 0.00037).

Comparing changes in the Functional Assessment Scale-Prostate subscale scores, radium-223 also improved quality of life especially in the pain, physical well-being, social/familial well-being, and emotional and functional well-being subscales.

In the study ALSYMPCA was documented a general higher incidence of grade 3–4 events in the placebo (62%) compared to the active arm (56%). In fact, with the exception of hematologic toxicities, solely the two adverse events anorexia (2% in radium-223 vs 1% of placebo) and decreased appetite (2 patients vs 0 patients) were more frequently associated with patients treated with radium-223. This is an important exception to the consuetude that the studies conducted in oncology report the highest incidence of grade 3–4 events associated with the treatment arm.

The most important grade 3 or higher toxicities associated with radium-223 were low myelosuppression (anemia, neutropenia, and thrombocytopenia) and low gastrointestinal rates (diarrhea, nausea, and vomiting).

In 2013, the FDA approved radium-223 for the treatment of patients with mCRPC with symptomatic bone metastases and unknown visceral metastatic disease.

6. Discussion

Before 2010, patients at this stage of disease, with an estimated survival of about 12 months, were almost considered terminally ill [75].

Existing therapies rely on a variety of therapeutic approaches with different mechanisms of action: drugs, immunologic, or radiopharmaceutical bone-targeted compounds, NSAIDs, opioids, and radiotherapy techniques that used either sequentially or in combination are able to relieve bone pain, prolong time to first SRE, and possibly extend survival (Table 1).

However, the availability of so many therapeutic approaches in a very short life span threatens to create several problems similar to those encountered in the recent past in the treatment of metastatic renal cell carcinoma (RCC). Following the introduction of targeted therapies, the scenario roughly shifted from a situation of a lack of therapeutic options or limited ones (e.g., cytokines) to one that has been described as an “embarrassment of richness” [76–79].

In the mCRPC landscape, physicians today have a number of options at their disposal so that, according to the patient clinical profile and physical conditions, they can freely choose the most suitable drug for a patient with bone metastases with the goals of achieving pain palliation, delayed SRE, and extended survival.

If the purpose of therapy is only pain palliation, the well-established WHO recommendations (Fig. 2) or radiotherapy are proven valid tools. However, if the goal of the therapy is
Table 3
Differences in α- and β-radionuclides used for therapy of patients with metastatic castration-resistant prostate cancer.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half life (d)</th>
<th>DNA damage</th>
<th>Linear energy transfer (nm)</th>
<th>No. of cells presumably hit by radiation</th>
<th>Anemia (%)</th>
<th>Bone marrow adverse events (grades 3–4)</th>
<th>Leucopenia (%)</th>
<th>Thrombocytopenia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strontium-89</td>
<td>11.4</td>
<td>Singlestrand breaks</td>
<td>2.4</td>
<td>240</td>
<td>8.5</td>
<td>5–12</td>
<td>7–27</td>
<td></td>
</tr>
<tr>
<td>Samarium-153</td>
<td>50.5</td>
<td>Singlestrand breaks</td>
<td>0.6</td>
<td>60</td>
<td>41</td>
<td>59</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Radium-223</td>
<td>1.9</td>
<td>Doublestrand breaks</td>
<td>0.05–0.1</td>
<td>5–10</td>
<td>13</td>
<td>2 (neutropenia)</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

b Phase 3 data are reported.

not just palliation, all the others drugs so far analyzed should be considered (Table 1).

Conversely, if the goal of the therapy is to delay the time to SRE or to increase survival, our personal opinion is that no clear recommendations are presently available. Similarly to RCC, the approach based on patient, drug, or disease features seems more appropriate.

With regard to prolonging survival, drugs available for first-line therapy following the progression of androgen-deprivation therapy are docetaxel, abiraterone, and sipuleucel-T. For second-line therapy after docetaxel failure, cabazitaxel, abiraterone, and enzalutamide are presently indicated (Table 4). Radium-223 is indicated for patients with bone metastases previously treated with docetaxel or considered unsuitable for this therapy. Tables 4–6 summarize the baseline characteristics, efficacy, and toxicities of the phase 3 trials carried out with each drug.

The first-line treatment with abiraterone in castration-resistant prostate cancer with ECOG PS 0-1 and no visceral metastases at baseline proved to be effective; sipuleucel-T showed similar efficacy only in a less advanced group of patients. Therefore, sipuleucel-T and abiraterone could be considered treatments of choice for asymptomatic patients or patients considered unsuitable for docetaxel or those refusing chemotherapy. In contrast, a docetaxel-based chemotherapy regimen appears more appropriate in patients with advanced or symptomatic rapidly progressing disease [75] because the outcome of the TAX 327 study showed that about 90% of asymptomatic patients presented bone metastases, 22% visceral metastases, and 13% Karnovsky PS less than 70.

The National Comprehensive Cancer Network guidelines recommend new drugs for second-line therapy after docetaxel instead of a docetaxel rechallenge. The latter was supported until 2010 due to the unavailability of subsequent lines of therapy [14]. The same guidelines report that in patients relapsing after first-line therapy with abiraterone and enzalutamide (presently available only for clinical trials), second-line therapy with the same drugs should be avoided due to the possibility of the onset of cross-resistance [80].

Considering the inclusion criteria of both phase 3 trials, abiraterone and enzalutamide could be indicated for patients without visceral disease, however, the exclusive preference of chemotherapy in the visceral metastases setting of CRPC patients should be re-evaluated. A valid criterion to differentiate the 2 drugs could be the absence of food interaction for enzalutamide and the lack of concomitant prednisone administration.

Cabazitaxel seems indicated for symptomatic patients or patients with liver metastases or rapidly progressing disease. Worth mentioning is the ability of cabazitaxel to overcome the blood–brain barrier, thus becoming a valid therapeutic option for patients with brain metastases.

The analyses of grades 3 and 4 toxicities observed in phase 3 studies (Table 6) indicate that cabazitaxel is not the most appropriate drug for patients with comorbidities associated with blood cell alterations (anemia, neutropenia). Moreover, cabazitaxel has not been evaluated in patients with liver function impairments [80].

Baseline conditions that could be considered critical for a therapy with enzalutamide and abiraterone are seizures and cardiovascular alterations, respectively, because in phase 3 trials these events resulted in comorbidities. However, it should be recognized that seizures and cardiovascular alterations are not considered absolute contraindications to use of enzalutamide and abiraterone.

Regarding radium-223, this drug induced a statistically significant clinical benefit, with a seemingly low toxicity profile in an outpatient setting of mCRPC patients. Thus we believe this radioisotope should not be classified like the other bone-seeking therapies used to treat pain or delay SRE in symptomatic patients. In addition, because the pivotal study showed that efficacy was observed in both groups of docetaxel-naïve and postdocetaxel patients, the drug should be evaluated as a viable monotherapy option in frontline or chemotherapy-progressed patients in the absence of visceral disease.

Concerning the opportunity to delay time to SRE, in agreement with other authors we believe that taxanes should be excluded. In fact, although cabazitaxel and docetaxel demonstrated improvement of survival, presently no robust data are available regardless the delay of SREs [81].

Finally, the choice of the drug should take into consideration the cost of therapy. Recent papers report costs ranging from a minimum of $20 000 for 10 cycles of docetaxel and the astronomical cost of $90 000 for sipuleucel-T administrations [82].

In the near future, important chances to extend benefit in terms of OS and SRE delay will be determined through drug...
### Table 4

Summary of efficacy of agents demonstrating improved overall survival in metastatic castration-resistant prostate cancer.

<table>
<thead>
<tr>
<th>Name</th>
<th>Docetaxel plus prednisone</th>
<th>Sipuleucel-T</th>
<th>Cabazitaxel plus prednisone</th>
<th>Abiraterone plus prednisone</th>
<th>Enzalutamide</th>
<th>Radium-223</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA indication</td>
<td>mCRPC (2004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3 (no. of patients)</td>
<td>TAX 327 (1006)</td>
<td>IMPACT (512)</td>
<td>TROPIC (755)</td>
<td>COU 301 (1195)</td>
<td>AFFIRM (1119)</td>
<td>ALSYMPCA (922)</td>
</tr>
<tr>
<td>Disease state</td>
<td>Chemo-naive CRPC</td>
<td></td>
<td>Chemo-naive CRPC</td>
<td>Post-docetaxel CRPC</td>
<td>Post-docetaxel CRPC</td>
<td>Bone metastases CRPC</td>
</tr>
<tr>
<td>Trial comparator</td>
<td>Prednisone + placebo</td>
<td>Placebo</td>
<td>Prednisone + placebo</td>
<td>Prednisone + placebo</td>
<td>Prednisone + placebo</td>
<td>Placebo and standard of care</td>
</tr>
<tr>
<td>Dosage and procedure of</td>
<td>75 mg/m² IV over 1 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>administration</td>
<td>every 3 wk + prednisone 5 mg orally bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS vs control data (mo)</td>
<td>19.2 vs 16.3</td>
<td>25.8 vs 21.7</td>
<td>15.1 vs 12.7</td>
<td>14.8 vs 10.9</td>
<td>18.4 vs 13.6</td>
<td>14.9 vs 11.3</td>
</tr>
<tr>
<td>HR</td>
<td>0.76</td>
<td>0.77</td>
<td>0.70</td>
<td>0.65</td>
<td>0.63</td>
<td>0.70</td>
</tr>
<tr>
<td>Reduction in death risk (%)</td>
<td>24</td>
<td>22</td>
<td>30</td>
<td>35</td>
<td>25</td>
<td>30</td>
</tr>
</tbody>
</table>

**Abbreviations:** FDA, Food and Drug Administration; HR, hazard ratio; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; NR, not recorded; OS, overall survival.

### Table 5

Baseline characteristics of the patients included in the phase 3 trial of agents demonstrating improved overall survival in metastatic castration-resistant prostate cancer.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Docetaxel plus prednisone</th>
<th>Sipuleucel-T</th>
<th>Cabazitaxel plus prednisone</th>
<th>Abiraterone plus prednisone</th>
<th>Enzalutamide</th>
<th>Radium-223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>NR (20% ≥ 75 y)</td>
<td>70</td>
<td>NR (28% ≥ 75 y)</td>
<td>NR</td>
<td>70</td>
<td>NR (28% &gt; 75 y)</td>
</tr>
<tr>
<td>≥65 yr of age (%)</td>
<td>NR (13% Karnovsky ≤ 70)</td>
<td>–</td>
<td>7</td>
<td>10</td>
<td>–</td>
<td>8.8</td>
</tr>
<tr>
<td>PS (ECOG) = 2 (%)</td>
<td>NR (22)</td>
<td>–</td>
<td>25</td>
<td>18</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Visceral disease (%)</td>
<td>NR (90)</td>
<td>–</td>
<td>80</td>
<td>89</td>
<td>NR</td>
<td>100</td>
</tr>
<tr>
<td>Bone disease (%)</td>
<td>NR (38)</td>
<td>–</td>
<td>–</td>
<td>NR</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Bone lesion ≥ 20 (%)</td>
<td>NR (41)</td>
<td>–</td>
<td>–</td>
<td>NR</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>PSA levels (ng/mL)</td>
<td>NR (146)</td>
<td>143.9</td>
<td>128.8</td>
<td>NR</td>
<td>107.7</td>
<td>146</td>
</tr>
<tr>
<td>Median (min–max)</td>
<td>(51.1–416)</td>
<td>(0.4–9253)</td>
<td>(0.2–11794.1)</td>
<td>(3.8–6026)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; NR, not recorded; PS, performance score; PSA, prostate-specific antigen.
In this regard, we agree with authors considering the association between abiraterone and radium-223 worthy of clinical evaluation because both drugs increased OS and delayed SRE through 2 very different mechanisms of action without inducing important toxicities [66].

In addition, phase 3 data on new drugs will soon be available. Specifically, cabozantinib appears very promising for patients with bone metastases in terms of pain reduction and the response rate observed at bone scan in phase 2 trials [83].

Conflict of interest statement

The authors have nothing to disclose.

Reviewers

Camillo Porta, M.D., IRCCS San Matteo University Hospital, Medical Oncology, Piazzale Golgi 19, I-27100 Pavia, Italy.

Giuseppe Procopio, M.D., Medical Oncologist, Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian 1, I-20133 Milan, Italy.

Acknowledgments

Editorial support was provided by Dragonfly Editorial and funded by Bayer SpA. The authors have received no honoraria or other form of financial support related to the development of this manuscript.

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