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Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer

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Abstract

Prostate cancer is the most prevalent urogenital malignancy. However, despite initial disease control using androgen deprivation, most of patients eventually develop progressive disease that is resistant to further hormone manipulation. For these patients with castration-resistant prostate cancer (CRPC), and particularly patients with metastatic disease, options have been limited, and prognosis is grim. However, as newer regimens and agents become available, higher rates of objective and biochemical response are being achieved, providing renewed hope for the management of these patients. With the aim of facilitating the treatment of these patients, the Spanish Oncology Genitourinary Group (SOGUG) has issued a series of the recommendations which have been collected in this review. Each recommendation is accompanied by the appropriate level of evidence and grade of recommendation on the basis of the characteristics of the data available.

Keywords: Antineoplasic protocols; Guidelines; Castration-resistant prostate cancer; Neoplasm; Treatment outcome

1. Introduction

Prostate cancer is the most prevalent male urogenital malignancy. For men with metastatic prostate cancer, hormonal therapy usually provides disease control for a substantial period of time, within a median of 18–24 months. However, the vast majority of patients eventually develop progressive disease that is resistant to further hormone manipulation. Until recently, cytotoxic chemotherapy was considered to be relatively ineffective in men with castration-resistant prostate cancer (CRPC). In early trials, objective response rates were 10–20%, and median survival generally did not exceed 12 months. However, newer regimens, particularly those that include docetaxel, are associated with higher rates of objective and biochemical (prostate-specific antigen [PSA]) response, as well as longer survival durations. Lastly, some new agents have shown significant results in well-performed, controlled medical trials.

In contrast, metastatic CRPC has become a more complicated disease to be properly treated; thus, the availability of updated clinical guidelines might be useful for physicians when it comes to decision-making. It is a concern of the Spanish Oncology Genitourinary Group (SOGUG) to issue recommendations for the optimal management of patients with CRPC patients. To address this issue, the Spanish Oncology Genitourinary Group (SOGUG) selected several of their members to issue recommendations for the treatment of patients with metastatic CRPC. First, a bibliographic search of articles published from 1980 to February 2011 was performed in the Medline database (PubMed) and the Cochrane Library using MeSH terms whenever possible. Search terms considered were "prostate cancer" OR "prostate neoplasms" AND "metastatic" OR "advanced" AND "castration resistant" OR "hormone refractory" AND "treatment" OR "management". Then, in a face-to-face working meeting held in March 15, 2011, the content and sections of the guideline were established, the group coordinators and members were selected, the working method to be followed was defined, and the deadlines were set. Before drafting of the manuscript, non-relevant or incomplete papers were discarded, and selected ones were evaluated using the Levels of Evidence and Grades of Recommendation modified from Sackett [1] (see Tables 1 and 2).

Finally, it is important to bear in mind that many patients with CRPC are older than 70 years. In older patients, CRPC should be managed according to their individual health status, which is conditioned mainly by the severity of associated comorbid conditions, level of independence and nutritional status, and not according to chronological age. Ideally, treatment options should be shaped by a thorough geriatric evaluation, as proposed by the International Society of Geriatric Oncology (SIOG) [2,3].

Table 1
Levels of evidence.

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

Modified from Sackett et al. [1].

Table 2
Grades of recommendation.

0 A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B	Based on well-conducted clinical studies, but without randomized clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

Modified from Sackett et al. [1].

Table 3
Definitions of castration-resistant prostate cancer, PSA progression and clinical progression by the PCWG2.

Definition of CRPC (patients must fulfill the following criteria)
– Clinical and/or PSA progression after castration with either orchidectomy or LHRH agonists
– Castration levels of serum testosterone (<50 ng/dL or <1.7 nmol/L)
– Progression despite anti-androgen withdrawal for at least 4–6 weeks
Definition of PSA progression
– Three consecutive PSA rises (1 week apart) resulting in two increases of 25% above the nadir, with a PSA level >2 ng/mL above the nadir
Definition of clinical progression
– Progression of bone lesions (two or more lesions on bone scan) or soft tissue progression using RECIST criteria

CRPC: castration-resistant prostate cancer; LHRH: luteinizing hormone-releasing hormone; PSA: prostate-specific antigen; PCWG2: Prostate Cancer Working Group 2; RECIST: Response Evaluation Criteria In Solid Tumors.

2. Definition of CRPC

Although most patients respond to initial suppression of gonadal androgens by medical or surgical castration, most of them eventually progress and develop a castration-resistant status. Various different terms have been used to describe prostate cancers that relapse after initial hormonal ablation therapy, including CRPC, androgen-independent cancers and hormone-independent cancers. This clinical situation includes patient cohorts with significantly different median survival times and different sensitivity to second hormonal manipulations, such as anti-androgen withdrawal, corticosteroids, estrogens, ketoconazol or abiraterone acetate. Although this group of CRPC patients progress to androgen deprivation, they might still be hormone-sensitive. The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) [4] defines CRPC as patients with serum castration levels of testosterone (testosterone <50 ng/dL or <1.7 nmol/L), PSA and/or clinical progression to castration, and progression despite anti-androgen withdrawal for at least 4–6 weeks. PSA progression is defined as three consecutive rises of PSA, 1 week apart, resulting in two 25% increases over the nadir, with a PSA level >2 ng/mL above the nadir. Clinical progression includes progression of bone lesions (two or more lesions on bone scan) or soft tissue progression using Response Evaluation Criteria In Solid Tumors (RECIST) criteria (Table 3). Also, the PCWG2 advises investigators not to delay the assessment of withdrawal in patients who have not responded or who have shown a decline in PSA levels for 3 months or less when antiandrogens have been administered in second or subsequent.

3. Continuing treatment with luteinizing hormone-releasing hormone analogs in patients with CRPC

Continuation of treatment with luteinizing hormone-releasing hormone (LHRH) analogs in patients with castration-resistant disease remains controversial, as exogenous testosterone has been demonstrated to exacerbate disease in the metastatic setting. Reports of clinical experiences in men who have progressed on endocrine therapy, and have been treated with chemotherapy, have shown an increase in PSA levels, with a subsequent decrease when androgen deprivation was reinstituted, suggesting that a persistent population of hormone-sensitive tumor cells persists despite overall progressive disease [5].

There are no prospective trials to demonstrate the impact of discontinuing androgen deprivation. Taylor et al. [6] carried out a retrospective multivariate analysis of 341 patients with CRPC in four different clinical trials. Continued androgen suppression was associated with a modest median survival benefit of 2–6 months; additionally, age, performance status, disease site and prior radiotherapy, which were also included in the model, were important prognostic factors for survival duration in these patients. Hussain et al. [7] preformed a review of 205 men treated on five consecutive Southwest Oncology Group (SWOG) phase II trials. They showed that continuous androgen suppression produced no obvious survival benefit; however, only 16% of patients were receiving androgen deprivation treatment.

Despite the lack of prospective clinical data, the PSA Working Group (PSAWG) recommended continuation of androgen suppression in all patients who have not undergone surgical castration as an eligibility criterion for phase II trials in the androgen-resistant setting [8]. In the absence of prospective data, the current recommendation is to maintain androgen deprivation therapy with LHRH analogs indefinitely in patients with CRPC.

Recommendation:

- LHRH analogs should be continued in patients with CRPC (level of evidence: III; grade of recommendation: C).

4. Secondary hormonal therapy

After failure of complete androgen blockade in metastatic prostate cancer, there are several treatment options that can be offered to patients before moving on to chemotherapy. However, their impact has not been established in randomized clinical trials, and the reported responses have not shown to be long lasting. Therefore, these therapies should be reserved for asymptomatic or oligosymptomatic patients, or for those with major contraindications for chemotherapy.

4.1. Antiandrogen withdrawal

Despite its poorly understood physiopathology, tumor responses to antiandrogen withdrawal have long been reported in the literature. The largest trial assessing this treatment modality was a multicenter study of 210 patients who

had failed to complete androgen blockade [9]. Although partial responses were seen only in 21% of cases and were not long lasting (median progression free survival was 3 months), 19% of patients remained progression-free for more than 1 year. A longer duration of antiandrogen use, a lower PSA at baseline, and PSA-only progression at study entry were associated with both longer progression-free survival and overall survival. Consequently, patients who fulfill these criteria should be considered to receive this approach [9]. The response can be delayed up to 6 or 8 weeks after the start of treatment withdrawal due to drugs' half-life.

4.2. Adrenal inhibition

Because the adrenal glands are a source of androgens, inhibition of their activity has been considered a potential therapy in prostate cancer for a long time. In this regard, the results of the phase III trial COU-AA-302, which will evaluate the efficacy of abiraterone in patients with metastatic CRPC before chemotherapy are awaited. At present, ketoconazole is the most widely used drug for this purpose. Ketoconazole is an antifungal agent belonging to the triazole family, which exerts its clinical effect through the inhibition of cytochrome P450 14a-demethylase, a catalyst of the conversion of lanosterol to cholesterol. This inhibition has demonstrated to reduce adrenal production of testosterone and yield responses in patients with prostate cancer.

The role of ketoconazole (400 mg three times a day, plus hydrocortisone 30 mg AM and 10 mg PM) plus antiandrogen withdrawal versus antiandrogen withdrawal alone was assessed in a phase III trial. Compared to androgen withdrawal alone, the addition of ketoconazole demonstrated significant benefits in terms of PSA (11% versus 27%, respectively; $p = 0.0002$) and objective responses (2% versus 20%, respectively; $p = 0.02$) [10].

However, the narrow therapeutic window of ketoconazole must be kept in mind; monitoring of hepatic function should be carried out routinely, and all drug interactions described for this compound must be taken care of. Co-administration of supplemental steroids, such as hydrocortisone, is strongly encouraged in order to avoid adrenal insufficiency. When dose reductions are needed, physicians should be aware that schedules with half the dose, for example ketoconazole 200 mg three times a day and hydrocortisone 20 mg AM and 10 mg PM, have reported similar results, although direct comparisons are lacking [11,12].

4.3. Corticosteroids

This group of drugs has long been used to induce medical adrenalectomy, although no impact on survival has been demonstrated. Probably the best information available to date is provided by phase III trials using corticosteroids as control arm [13,14]. Prednisone can achieve 21% of PSA response and three to 4 months of time to progression.

Recommendations:

- Antiandrogen withdrawal should be considered in most patients with CRPC, except in symptomatic patients or in those who show a quick and aggressive progression (level of evidence: IIb; grade of recommendation: B).
- Ketoconazole plus hydrocortisone and antiandrogen withdrawal produces a greater number of partial responses than antiandrogen withdrawal alone, and is an option in asymptomatic CRPC (level of evidence: IIa; grade of recommendation: B).

5. Sipuleucel-T

Sipuleucel-T is an active cellular immunotherapy consisting of autologous peripheral-blood mononuclear cells, including antigen-presenting cells, which have been activated ex vivo with a recombinant fusion protein known as PA2024. This fusion protein in turn consists of human prostatic acid phosphatase fused to granulocyte-macrophage colony-stimulating factor.

A small, randomized study of sipuleucel-T compared to placebo demonstrated a significant reduction of 41% in the relative risk of death [15]. Another randomized, placebo-controlled study showed a trend toward increased survival with sipuleucel-T therapy, although it was not statistically significant [16]. Neither study could demonstrate a significant effect regarding the primary endpoint, which was time to disease progression.

To evaluate the survival benefit of sipuleucel-T treatment in CRPC patients a multicenter, double-blind, placebo-controlled phase III trial was performed (IMPACT trial) [17]. Five hundred and twelve patients were randomized in a 2:1 ratio to receive either sipuleucel-T or placebo, administered intravenously every 2 weeks, for a total of three infusions. The primary endpoint was overall survival. Only patients with asymptomatic disease were enrolled. Exclusion criteria included visceral metastases, pathologic fractures of long bones, spinal cord compression, and treatment within the previous 28 days with systemic glucocorticoids, external beam radiation, surgery, or systemic therapy for prostate cancer (except medical or surgical castration). Patients were scheduled for three leukapheresis procedures (at weeks 0, 2, and 4), each followed approximately 3 days later by infusion of sipuleucel-T or placebo. Sipuleucel-T was prepared at a central manufacturing facility. The median survival was 4.1 months longer in the sipuleucel-T group (25.8 months) than in the placebo group (21.7 months), yielding an adjusted hazard ratio (HR) for death was 0.78 (95% confidence interval [CI]: 0.61–0.98), and a relative reduction in the risk of death of 22% ($p = 0.03$). The treatment effect was not explained by differences between the two study groups in the subsequent use of docetaxel. The time to objective disease progression was similar in the two study groups. The most common adverse events in the sipuleucel-T group, within 1 day after

infusion, were chills (51.2%), fever (22.5%), fatigue (16.0%), nausea (14.2%), and headache (10.7%).

Currently, sipuleucel-T treatment is not approved for use in Europe, but if regulatory approval is obtained, in the future it might be considered for the treatment of patients with asymptomatic metastatic CRPC before docetaxel therapy. Nevertheless, several issues have raised concerns that preclude the generalized use of sipuleucel-T, including that its exact mechanism of action is not entirely clear, that it involves a complex method of administration and that it is an expensive treatment given its modest effect on tumor response of tumor progression [18].

Recommendation:

- Sipuleicel-T is a treatment option in asymptomatic patients with metastatic CRPC before chemotherapy with docetaxel if regulatory approval is obtained (level of evidence: Ib; grade of recommendation: A).

6. First-line chemotherapy with docetaxel

Docetaxel was approved in 2004 for the treatment of men with metastatic CRPC based on two large multicenter randomized clinical trials [19–21]. The TAX327 study randomized 1006 patients to receive either docetaxel in a three-weekly schedule, docetaxel in a weekly schedule or mitoxantrone, the three of them given with low-dose prednisone. The SWOG 9916 study randomized 770 patients to either docetaxel in combination with estramustine phosphate, or mitoxantrone plus prednisone. In both studies, the primary endpoint was overall survival. The TAX327 study showed an improvement in overall survival of 2.4 months improved quality of life, better pain control, a decrease in PSA, and objective tumor response in the group of patients treated with the three-weekly schedule of docetaxel. The second study had similar results regarding overall survival and PSA response, but did not show any improvement in quality of life and pain control. Up to 10 cycles of treatment were planned in the TAX327, and most patients received the prescribed doses in the docetaxel every-three-week's schedule. On the basis of these evidences, and given that docetaxel plus estramustine phosphate showed a worse toxicity profile, docetaxel every 3 weeks plus prednisone is considered the standard of care in metastatic CRPC. Moreover, the SWOG has considered it the standard arm in their clinical trials.

A posterior analysis of the TAX327 was conducted on 110 minimally symptomatic or asymptomatic men at baseline, as defined by quality of life. The median survival for this group of men was 25.6 months compared with 17.1 months for patients who referred more symptoms ($p = 0.009$). Differences in overall survival between the three treatment arms among minimally symptomatic and asymptomatic patients reflected the differences observed in the whole group, although they did not reach statistical significance due to the small number of individuals [22]. This finding opens a question about the benefit of treating all patients with metastatic CRPC with chemotherapy or only those that are symptomatic. Again, the analysis of the data from the TAX327 trial may help us answer this question.

Table 4
Novel independent prognostic variables metastatic castration-resistant prostate cancer identified in the TAX327 trial.

Variable	Hazard ratio	*p*
Liver metastases	1.66	0.019
Number of metastatic sites	1.63 (if <2)	0.001
Clinically significant pain	1.48	<0.0001
Karnofsky performance status	1.39 (if <80)	0.016
Type of progression:		
Measurable disease	1.37	0.005
Bone scan	1.29	0.01
Pretreatment PSA doubling time	1.19 (if <55 days)	0.066
PSA level	1.17 (per log rise)	<0.0001
Tumor grade	1.18 (for high grade)	0.069
Alkaline phosphatase level	1.27 (per log rise)	<0.0001
Hemoglobin level	1.11 (per unit decline)	0.004

PSA: prostate-specific antigen.

A prognostic nomogram for patients with metastatic CRPC has been built using data from the TAX327 trial, with the purpose of developing a multivariate model to identify novel independent prognostic variables [23]. By multivariate analysis, 10 independent prognostic factors other than treatment group were identified. These are shown in Table 4. On the basis of these, results we recommend that all patients with symptomatic metastatic CRPC should be treated with docetaxel in a three-weekly schedule, plus prednisone.

Patients with minimally symptomatic or asymptomatic metastatic CRPC might be treated with the same docetaxel schedule, particularly if other factors of poor prognosis are present, such as more than two metastatic sites, a high Gleason score, a PSA doubling time of less than 55 days (specially in patients with high baseline PSA levels), a low hemoglobin count, high alkaline phosphatase levels and high baseline PSA levels.

Patients with asymptomatic or minimally symptomatic disease, and without any of these poor prognosis characteristics, could be candidates to be included in clinical trials evaluating new hormonal or immune therapeutic agents, or might be considered to be treated with secondary hormonal treatments such as prednisone or ketoconazole. PSA response to secondary hormonal treatments has been associated with survival, may delay the start of chemotherapy or even replace it in some circumstances [10].

Recommendations:

- Docetaxel in a three-weekly schedule (75 mg/m^2), plus prednisone (5 mg bid), is considered the standard first-line chemotherapy in metastatic CRPC (level of evidence: Ia; grade of recommendation: A).
- All patients with symptomatic metastatic CRPC should be treated with docetaxel in a three-weekly schedule, plus prednisone (level of evidence: Ia; grade of recommendation: A).

- Asymptomatic patients with metastatic CRPC might be treated with the same docetaxel schedule, particularly if additional factors of poor prognosis are present (level of evidence: Ia; grade of recommendation: A).

7. Treatment options after docetaxel

7.1. Abiraterone

Abiraterone acetate is an inhibitor of the enzyme CYP17 that blocks androgen synthesis in the testes, adrenals and in the tumor itself [24]. As a result, plasma testosterone levels are significantly lower than those achieved with conventional hormone therapies; in addition, a reduction in intratumoral levels of androgens is obtained.

The safety and activity of abiraterone was tested in a dose-escalation trial of 21 patients with progressive prostate cancer [25]. Maximal endocrine effects were observed with 750 and 1000 mg doses of abiraterone, which were chosen for subsequent phase II trials. Although this was a phase I trial, clinical response to abiraterone was favorable, with 57% of patients achieving a reduction in PSA levels of more than 50% lasting more than 3 months.

Antitumor activity of abiraterone in post-docetaxel patients was initially tested in a phase II study that included 47 patients [26]. A 50% reduction in PSA levels was observed in 51% (24 of 47) of patients. In another phase II trial that enrolled 58 patients with metastatic CRPC whose disease had progressed following chemotherapy with docetaxel [27], a decrease in PSA levels of more than 50% was confirmed in 36% ($n = 22$) of patients. The incidence of mineralocorticoid-related toxicities, such as hypertension or hipokalemia, was reduced by adding low-dose prednisone. Encouraging results from these early studies led to the design of larger phase III trials. The COU-AA-301 randomized a total of 1195 patients with docetaxel-refractory CRPC to either abiraterone or placebo in a 2:1 fashion. Both arms received concomitant prednisone therapy [28]. Patients were stratified by the Eastern Cooperative Oncology Group (ECOG) performance status (0–1 versus 2), number of lines of prior chemotherapy (1 versus 2), pain score, and the nature of progression (defined by PSA, radiograph, or both). The primary endpoint was overall survival. Secondary efficacy endpoints included time to PSA progression, PSA response rate, and radiographic progression-free survival.

Median age of the study participants was 69 years. Only a small proportion of patients had an ECOG 2 (10.8%) or had received two lines of prior chemotherapy (28.3%). Treatment with abiraterone resulted in a significant improvement in overall survival from 10.4 to 14.8 months ($p < 0.0001$), and a survival benefit was observed across all subgroups. Abiraterone therapy also yielded superior outcomes with respect to time to PSA progression (10.2 versus 6.6 months; $p < 0.0001$), radiographic progression-free survival (5.6 versus 3.6 months; $p < 0.0001$) and PSA response rate (29.1% versus 5.5%; $p < 0.0001$). Several grade 3–4 toxicities were more frequent in abiraterone treated patients, including fluid retention (2.3% versus 1.0%), hypokalemia (3.8% versus 0.8%), hypertension (1.3% versus 0.3%) and cardiac disorders (4.1% versus 2.3%).

Recommendation:

- Treatment with abiraterone should be considered for patients with metastatic CRPC following progression with docetaxel (level of evidence: Ib; grade of recommendation: A).

7.2. Cabazitaxel

Cabazitaxel is a new tubulin-binding taxane that has shown to be as potent as docetaxel in cell lines. Moreover, cabazitaxel has demonstrated antitumor activity in models resistant to paclitaxel and docetaxel due to its poor affinity for the ATP-dependent drug efflux pump, P-glycoprotein, member of the multidrug resistance protein family, which confer both constitutive and acquired resistance to taxanes [29].

Phase I clinical studies have shown that neutropenia is the primary dose-limiting toxicity of cabazitaxel. Thus, the dose recommended for further development in phase II trials was 20–25 mg/m^2 [30].

To evaluate the survival benefit with cabazitaxel treatment in docetaxel-refractory CRPC, a randomized, multicenter, multinational phase III trial, the TROPIC trial, was performed [31]. Seven hundred and fifty-five patients were randomly assigned in a 1:1 ratio to receive either cabazitaxel (25 mg/m^2 intravenously over 1 h) or mitoxantrone (12 mg/m^2 intravenously over 15–30 min) on day one of each 21-day cycle. All patients received oral prednisone 10 mg daily or similar doses of prednisolone where prednisone was unavailable. To be included, patients had to have documented disease progression during or after completion of docetaxel treatment, and an ECOG performance status of 0–2. Patients were stratified according to disease measurability (measurable versus non-measurable) and ECOG performance status (0–1 versus 2). Treatment was continued for a maximum of 10 cycles. Prophylactic granulocyte colony-stimulating factor was not allowed during the first cycle, but was allowed (at physicians' discretion) after the first occurrence of neutropenia lasting 7 days or more, or neutropenia complicated by fever or infection. The primary endpoint was overall survival. Secondary endpoints included progression-free survival, PSA response, PSA progression, objective tumor response, pain response, pain progression and time to tumor progression.

Roughly, 50% of patients had measurable soft-tissue disease, and 25% had visceral (poor prognosis) disease. Median overall survival was 15.1 months in the cabazitaxel group versus 12.7 months in the mitoxantrone group. This result corresponds to a 30% reduction in the relative risk of death (HR: 0.70; 95% CI: 0.59–0.83; $p < 0.0001$). Median progression-free survival was 2.8 months in the cabazitaxel group and 1.4 months in the mitoxantrone group (HR: 0.74;

95% CI: 0.64–0.86; $p < 0.001$). Patients treated with cabazitaxel had significantly higher rates of tumor response (14.4% versus 4.4%) and PSA response (39.2% versus 17.8%). Pain response rates were similar in the two groups, and there were no significant differences between treatments groups regarding time to pain progression.

The most common adverse effects of cabazitaxel were hematological. Grade 3 or higher neutropenia occurred in 82% of patients, of which 8% were febrile neutropenia; leucopenia and anemia occurred in 68% and 11% of patients, respectively. The most common non-hematological grade 3 or higher adverse event was diarrhea (6%). Five percent of cabazitaxel treated patients and 2% of mitoxantrone treated patients died within 30 days of the last infusion. The most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences.

Cabazitaxel is the first chemotherapy treatment to improve survival in patients with metastatic CRPC with progressive disease after docetaxel-based treatment.

Following recommendations of the 2006 Update of American Society of Clinical Oncology (ASCO) Practice Guideline Recommendations for the Use of White Blood Cell Growth Factors [32], we recommend the use of primary prophylaxis with colony-stimulating factors (CSF) for the prevention of febrile neutropenia in patients with certain clinical factors that predispose them to an increased risk of infection-associated complications from prolonged neutropenia. Upfront prophylaxis with CFS may be necessary in patients aged 65 years or more who have had episodes of febrile neutropenia in a previous treatment with docetaxel, extensive prior radiotherapy treatment with bone marrow involvement by tumor-producing cytopenias, poor nutritional status, and the presence of open wounds or active infections.

Recommendation:

- Cabazitaxel should be considered for the treatment of patients with metastatic CRPC with progressive disease after docetaxel-based treatment (level of evidence: Ib; grade of recommendation: A).

8. Docetaxel rechallenge and other chemotherapy treatments

Patients with CRPC treated with docetaxel plus prednisone usually progress after 6–8 months. Until recently, there was no standard option for salvage chemotherapy, and patients were usually retreated with the same docetaxel schedule ('rechallenge'), or received mitoxantrone, vinorelbine, metronomic schedules or palliative care. Docetaxel rechallenge may be an option for patients who have progressed after having previously responded, and who did not experience any severe toxicity. In retrospective studies, docetaxel rechallenge appeared to be of more benefit in patients who were retreated after a period of at least 3 months since the last cycle of first-line docetaxel. These studies showed a decline in PSA levels of 50% in almost half of patients, a median progression-free survival of 4–6 months and a median overall survival of 16 months. Tolerance was acceptable and there were no toxicity-related deaths [33–35].

In a prospective phase II study, patients who initially responded and then progressed after a period of biochemical remission of at least 5 months (range: 5–10 months), and who were not receiving corticosteroids before the rechallenge, were retreated with docetaxel 75 mg/m^2 every 3 weeks plus oral prednisone 10 mg daily. The results were worse than previously reported in retrospective studies: a decrease of 50% in PSA levels was observed in 24.5% of patients, median progression-free survival was 5 months and the median overall survival since enrollment was 13 months.

Despite these results, docetaxel rechallenge is considered an active treatment. The observed rate of severe neutropenia is lower than that described for cabazitaxel. Thus, rechallenge with docetaxel can be considered an option for patients who require chemotherapy but show significant cabazitaxel-related toxicity [36].

Many oncologists have used mitoxantrone in combination with prednisone in patients who have progressed on docetaxel. In the late 90s, two pivotal studies showed that mitoxantrone combined with low dose corticoids was superior to corticoids in terms of palliative effect, on the basis of pain response [13,14]. However, neither study demonstrated mitoxantrone to be superior to palliative corticosteroid therapy. This combination was used as the control arm in the TROPIC phase III trial. In this study, mitoxantrone plus prednisone was better tolerated but inferior to cabazitaxel plus prednisone in terms of overall survival. In this heavily pretreated population, mitoxantrone plus prednisone produced a PSA response rate in 18% of patients, and pain response in 8% of patients; median progression-free survival was 1.4 months and median overall survival was 12.7 months.

Encouraging results with alternative treatments, including vinorelbine and oral cyclophosphamide, have been obtained in prospective clinical phase II trials. The lack of representative randomized phase III trials and unknown long-term efficacy are the major problems associated with all these studies (level of evidence: IIb; grade of recommendation: B). Vinorelbine is a semi-synthetic vinca alkaloid that has undergone phase II studies in CRPC. Single-agent studies have shown a decrease of more than 50% in PSA levels that was sustained for three to 4 weeks in 13–17% of evaluable patients. Also, a durable clinical benefit, as defined by improvement in pain index and/or performance status, was observed in 32–39% of patients. Toxicity was moderate, and was mainly hematological, with grade 3–4 neutropenia reported in 51% of patients receiving vinorelbine at 25 mg/m^2/week, and 20% of patients receiving the drug on days one and eight of a 3-week cycle. The results of a randomized clinical trial comparing vinorelbine plus hydrocortisone with hydrocortisone alone in 414 patients with CRPC who progressed after primary hormonal therapy, suggest a

palliative effect comparable to that achieved with mitoxantrone plus prednisone [37].

Intravenous cyclophosphamide has been tested in many trials. However, currently there is interest in oral cyclophosphamide, which seems to be less toxic than intravenous cyclophosphamide and may have greater activity. In a phase II study, 23 patients were treated with metronomic oral cyclophosphamide and 10 mg prednisolone daily until disease progression. Tolerance to treatment, and effects on PSA levels and pain, were assessed. Low dose metronomic cyclophosphamide plus prednisolone was safe, well-tolerated and demonstrated interesting clinical activity. A decrease of more than 50% in PSA levels occurred in 26% of patients, and favorable palliative effects on pain were observed in 43% of patients. Median progression free survival was 6 months (95% CI: 4–8) and median overall survival was 11 months [38]. Because of its oral administration, low cost and lack of toxicity, this treatment might be a viable alternative in selected patients of older age or with several comorbidities.

Recently, results from AFFIRM trial comparing MDV3100, a rationally designed molecule to target androgen-receptor signaling, with placebo in men with advanced prostate cancer who were previously treated with docetaxel-based chemotherapy have been released. A planned interim analysis of the AFFIRM trial revealed that estimated median survival was 18.4 months for men treated with MDV3100, compared with 13.6 months for men treated with placebo ($p < 0.0001$). This data translates into a 37% reduction in the risk of death with MDV3100 (HR: 0.63).

Recommendation:

- Alternative treatments after docetaxel and/or cabazitaxel and/or abiraterone include docetaxel rechallenge, mitoxantrone, oral cyclophosphamide or vinorelbine chemotherapy (level of evidence: IIb; grade of recommendation: B).

9. Bone targeted treatments

Osteoclast-mediated bone resorption is inhibited by bisphosphonates. In patients with bone metastases from CRPC, zoledronic acid treatment is recommended to diminish skeletal-related events, which included pathological fractures, spinal cord compression, and severe bone pain requiring palliative radiation therapy or bone surgery. To date, no data is available about if other bisphosphonates exert a similar activity.

In a phase III trial, 643 patients with CRPC and a history of bone metastases were randomly assigned to a 15 month treatment of intravenous zoledronic acid at 4 mg ($n = 214$), zoledronic acid at 8 mg (subsequently reduced to 4 mg) ($n = 221$), or placebo ($n = 208$) every 3 weeks [39,40]. All patients were in androgen deprivation therapy, and other antineoplastic treatments at study entry or during the trial were given at the discretion of the treating physician. The primary efficacy variable was the proportion of patients having at least one skeletal-related event.

The results showed that more patients who received placebo suffered from skeletal-related events compared to those who received zoledronic acid at 4 mg (44.2% versus 33.2%; difference: −11.0%; 95% CI: −20.3% to −1.8%; $p = 0.021$). Also, significantly fewer patients who received zoledronic acid at 4 mg experienced a fracture (22.1% versus 13.1%, $p = 0.015$). Median time to the first skeletal-related event was longer in patients treated with zoledronic acid than in patients who received placebo (488 versus 321 days; $p = 0.01$) [40]. No differences were observed in overall survival between study groups.

The recommended dose regimen of zoledronic acid is 4 mg separated by a minimum of 3 weeks. Suplemental calcium and vitamine D is recommended. In patients with altered renal function (i.e. creatinine clearance between 30 and 60 mL/min), the dose of zoledronic acid should be reduced. Treatment is not recommended in patients with a creatinine clearance lower than 30 mL/min. Dental and maxilar examination by a specialist is recommended before bisphosphonate treatment to diminsh the risk of osteonecrosis [41]. This risk is higher in patients with a history of tooth extraction, poor oral hygiene, or use of a dental appliance.

RANKL is the main driver of osteoclast formation, function, and survival. Denosumab is a human monoclonal antibody directed against RANKL that inhibits osteoclast-mediated bone destruction. In a phase III study, men with CRPC and no previous exposure to intravenous bisphosphonates were randomized to receive 120 mg subcutaneous denosumab plus intravenous placebo, or 4 mg intravenous zoledronic acid plus subcutaneous placebo, every 4 weeks [42]. Supplemental calcium and vitamin D were strongly recommended. The primary endpoint was time to first on-study skeletal-related event. Overall, 1904 patients were randomized to denosumab ($n = 950$) and zoledronic acid ($n = 951$). The median time to first on-study skeletal-related event was 20.7 months (95% CI: 18.8–24.9) for denosumab compared with 17.1 months (95% CI: 15.0–19.4) for zoledronic acid (HR: 0.82; 95% CI: 0.71–0.95; $p = 0.0002$ for non-inferiority; $p = 0.008$ for superiority).

Serious adverse events were recorded in a similar proportion in both arms (63% in the denosumab arm versus 60% in the zoledronic acid arm). More events of hypocalcemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; $p < 0.0001$). Osteonecrosis of the jaw occurred infrequently but more frequently in denosumab treated patients (22 [2%] versus 12 [1%]; $p = 0.09$). Denosumab showed to be better than zoledronic acid for the prevention of skeletal-related events, and represents a novel potential treatment option for the prevention of skeletal complications in patients with metastatic CRPC. Denosumab has no effect on renal function and no need for renal monitoring. Denosumab is not yet available in Europe, but it is expected to be approved soon.

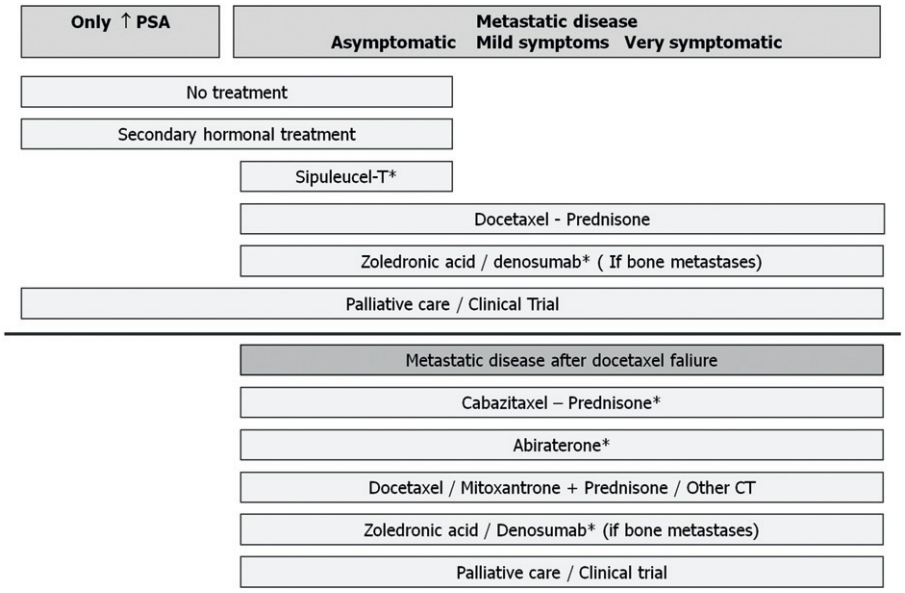

Fig. 1. Treatment algorithm for patients with metastatic castration-resistant prostate cancer. CT: chemotherapy; PSA: prostate-specific antigen. *Not approved for use by the European Medicines Agency.

Recommendation:

- Bone targeted treatments zoledronic acid (4 mg intravenously every 3–4 weeks) or denosumab (120 mg subcutaneously every 4 weeks; if approved by regulatory authorities) are recommended for the treatment of bone metastases in patients with CRPC to prevent bone complications (level of evidence: Ib; grade of recommendation: A).

10. Radionuclides and palliative treatments

Bone-targeted systemic radionuclides have become viable treatment options for patients with CRPC and multiple, painful bone metastases. They are particularly useful in patients who have relapsed following an initial course of hormonal or cytotoxic chemotherapy, and also in patients with progressive or recurrent symptoms at the treated sites after treatment with external beam radiation.

Three radionuclides are currently approved for the treatment of bone pain: first-generation phosphorus-32, second-generation strontium-89, and third-generation samarium-153. These radionuclides localize into regions of enhanced bone turnover, where they deliver high local doses of radiation through the emission of beta particles. Beta particle emissions from phosphorus-32 and strontium-89 have a higher energy level than samarium-153, and result in greater bone marrow toxicity. The half-life of samarium-153 is 1.9 days, much shorter than that of the other two agents (14.3 and 50.5 days, respectively), and results in a more rapid delivery of radiation.

When used after palliative radiotherapy treatment, strontium-89 demonstrated a significant improvement of time to pain recurrence compared with placebo in a randomized trial (level of evidence: 1b; grade of recommendation: A) [43]. However, this result was not confirmed in a subsequent smaller randomized trial.

Extensive data from multicentric, prospective, randomized, controlled clinical trials currently support the use of samarium SM 153 lexidronam in patients with castration-resistant disease and painful bone metastases. Pain relief and a decrease in analgesic consumption is expected in the majority of patients treated (level of evidence 1b; grade of recommendation: A) [44,45]. Compared with strontium-89, the potential advantages of samarium SM 153 lexidronam include a short half-life and mild hematologic toxicity.

The only clinically significant toxicity reported with samarium SM 153 lexidronam is mild and transient myelosuppression. White blood cell and platelet counts decrease beginning at 1–2 weeks after the start of treatment to approximately 50% of the baseline level at three to 5 weeks post-administration. Recovery to pretreatment levels is typically observed by the eighth week. Non-hematologic adverse events occur at similar rates in patients who receive placebo and 1.0 mCi/kg of active drug.

Repeated dosing of samarium SM 153 lexidroman for the treatment of bone metastases is both efficacious and well tolerated, and may be considered a reasonable treatment option in patients whose bone pain recurs after an initial dose. Repeated doses can be used in patients whose bone marrow reserve is adequate at the time of administration. Pain responses after repeated dosing are similar in magnitude and frequency to those observed after an initial dose [46].

Currently, radioisotopes can be offered to patients with positive bone scans and osteoblastic lesions, in patients with multifocal disease with refractory bone pain due to cancer,

and in patients with good marrow reserve that show progression of bone pain despite hormonal treatment, chemotherapy, or radiotherapy.

Both strontium-89 and samarium-153 have shown to decrease, partially or completely, bone pain in up to 70% of patients. Samarium SM 153 lexidroman is the most widely radioisotope used today in clinical practice at doses of 1.0 mCi/kg. Advantages include a short half-life and mild hematologic toxicity. Repeated doses can be used in patients who have shown previous response. The relative contraindications for its use are predominant soft-tissue pain, unifocal bone lesions, predominant osteolytic lesions (poor uptake on the bone scan). The use of both radioisotopes is contraindicated in patients with severe bone marrow suppression or severe renal dysfunction.

Recently, preliminary results from the ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer patients; NCT00699751) phase III trial evaluating the efficacy and safety of Alpharadin (radium-223 chloride) compared with placebo in patients with CRPC with symptomatic bone metastases, were presented at the European Multidisciplinary Cancer Congress (ECCO ESMO ESTRO) on September, 2011. The results showed that Alpharadin produced as significant improvement in the median overall survival compared with placebo (14.0 versus 11.2 months; two-sided p-value = 0.0022, HR: 0.699) in chemotherapy naïve patients as well as those previously treated with docetaxel [47].

Finally, palliative treatment should be initiated whenever deemed necessary, and should include pain and symptoms management, radiotherapy for patients with painful metastasis, palliative urological surgery and/or surgical management of spinal cord compression.

Recommendations:

- When used after radiotherapy palliative treatment, strontium-89 has demonstrated a significant improvement of time to pain recurrence (level of evidence: Ib; grade of recommendation: A).
- In patients with castration-resistant disease and painful bone metastases, samarium SM 153 lexidronam offers pain relief and decreases analgesic consumption (level of evidence: Ib; grade of recommendation: A).

11. Conclusions

With the purpose of helping clinicians in the treatment of CRPC, the SOGUG has issued a series of recommendations based on the available evidence. In summary, the first-line treatment options for patients with metastatic CRPC are: a secondary hormonal treatment, treatment with sipuleucel-T (if available), docetaxel plus prednisone, and zoledronic acid or denosumab (if available) if bone metastases are present. Either palliative care or inclusion in a clinical trial must always be considered. After docetaxel failure, second-line treatment options include: cabazitaxel plus prednisone (when available), abiraterone (when available). Other treatment possibilities include docetaxel, mitoxantrone plus prednisone or other chemotherapy treatments, and zoledronic acid or denosumab (if available) if bone metastases are present. Either palliative care or inclusion in a clinical trial must be considered (Fig. 1).

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Conflict of interest statement

The authors declare that they do not have any conflicts of interest that could inappropriately influence their work.

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