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

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Summary

Prostate cancer is the most prevalent male urogenital malignancy. Approximately 30% of patients with prostate cancer will develop advanced disease. Androgen deprivation therapy achieves disease control in about 90% of these patients, but the majority of them will eventually develop progressive disease, a status called castration-resistant prostate carcinoma (CRPC). However, in recent years, several new therapy strategies, such as immunotherapy, hormonal manipulations, chemotherapy agents and some bone-targeted therapies, have demonstrated an improvement in terms of overall survival in controlled trials. In 2012, the Spanish Oncology Genitourinary Group (SOGUG) published its recommendations for the treatment of patients with CRPC. Due to the recent appearance of important new data and the complexity of decision-making in this field, SOGUG herein provides updated recommendations for the treatment of patients with metastatic prostate cancer.

Keywords: Asymptomatic; Castration-resistant prostate carcinoma; Chemotherapy; Hormonal therapies; Recommendations; Symptomatic

1. Introduction

Prostate cancer is the most prevalent male urogenital malignancy. In 2012, 416,732 new cases of prostate cancer were diagnosed in Europe, with 27,853 cases in Spain. Age-standardized incidence and mortality per 100,000 inhabitants per year were 96.0 and 19.3 in Europe and 96.8 and 15.2 in Spain, respectively [1]. Approximately 30% of patients with prostate cancer will develop advanced disease. Androgen deprivation therapy (ADT) achieves disease control in about 90% of these patients, for a median of 18–24 months, but the majority eventually will develop progressive disease, a status called castration-resistant prostate carcinoma (CRPC). In 2004, the combination of docetaxel and prednisone demonstrated an improvement in overall survival (OS) [2]. Since then, several new strategies such as immunotherapy, hormonal manipulations, chemotherapy agents and some bone-targeted therapies have also demonstrated an improvement in OS in controlled trials.

In 2012, the Spanish Oncology Genitourinary Group (SOGUG) published its recommendations for the treatment of patients with CRPC. Due to the recent appearance of important new data and the complexity of making decisions in this field, SOGUG has decided to update its recommendations based on the information available up to September 2014. Structure and content of the guideline, the working method and the deadlines were established by a committee. The members responsible for each section reviewed the *status quo* and recent advances in their section and prepared a draft of recommendations. Levels of Evidence and Grades of Recommendation modified from Sackett were included [3]. All authors agreed on the final content of the document.

2. Definition of castration-resistant prostate cancer

Although the majority of patients with advanced prostate cancer respond to initial suppression of gonadal androgens by medical or surgical castration, most eventually progress and reach castration-resistant status. CRPC is defined as disease progression (as demonstrated by increased prostate-specific antigen [PSA] levels in serum, new clinical metastases, or progression of existing metastases) despite the administration of ADT. The Prostate Cancer Clinical Trials Working Group 2 (PCWG2) [4] defines patients with CRPC as patients with serum castration levels of testosterone (testosterone <50 ng/dL or <1.7 nmol/L), PSA progression and/or clinical progression to castration, or progression despite anti-androgen withdrawal for at least 4–6 weeks.

PSA progression is defined as three consecutive rises in serum PSA levels, 1 week apart, resulting in 25% increases over the nadir value, with a PSA level >2 ng/mL above the nadir level. Clinical progression includes progression of bone lesions (2 or more lesions on bone scan) or soft tissue progression using Response Evaluation Criteria in Solid Tumors (RECIST). The PCWG2 advises investigators not to delay new treatment after withdrawal in patients who have not responded to previous treatment, or who have shown a decline in PSA levels for 3 months or less when anti-androgens have been administered in second

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or subsequent treatment lines. CRPC includes patients without metastases or symptoms with rising PSA levels despite the use of ADT, as well as patients with metastases.

2.1. Continuing treatment with luteinizing hormone-releasing hormone analogs in patients with castration-resistant prostate cancer

When disease progresses, discontinuation of luteinizing hormone-releasing hormone (LHRH) analogs therapy can result in an increase in serum testosterone and, thus, contribute to disease progression. Continuation of treatment with LHRH analogs in patients with castration-resistant disease remains controversial, but exogenous testosterone has been demonstrated to exacerbate disease in the metastatic setting.

There are currently no prospective trials demonstrating the impact of discontinuing ADT. Taylor et al. carried out a retrospective multivariate analysis of 341 patients with CRPC in 4 clinical trials [5]. Continued androgen suppression was associated with a modest median survival benefit of 2–6 months. In contrast, Hussain et al. conducted a review of 205 men treated in 5 consecutive SWOG phase II trials [6]. They showed that continuous androgen suppression produced no obvious survival benefit. Despite the lack of prospective clinical data, the PSA Working Group (PSAWG) recommended the continuation of androgen suppression in all patients as an eligibility criterion for phase III trials in the androgen-resistant setting [7].

Recommendation:

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

2.2. Antiandrogen withdrawal

For patients receiving an antiandrogen agent as part of a combined androgen blockade regimen, the discontinuation of the antiandrogen treatment may result in a clinical or biochemical (PSA) response. Despite its pathophysiology being poorly understood, tumor responses to antiandrogen withdrawal have been reported in the literature for many years. Partial responses have been detected in only 21% of cases, and these were not long-lasting (median progression-free survival [PFS] was 3 months), while 19% of patients remained progression-free for more than 1 year [8]. Based upon these observations, the first therapeutic approach in a patient presenting progression following ADT is generally the discontinuation of his current antiandrogen therapy. If asymptomatic, alternative therapy should not be initiated until response has been ruled out.

Recommendation:

- Antiandrogen withdrawal should be considered in most patients with CRPC, except in symptomatic patients or in those who are showing rapid and aggressive progression (level of evidence: IIb; grade of recommendation: B).

3. Asymptomatic or minimally symptomatic patients with metastatic castration-resistant prostate cancer (mCRPC)

To date, 3 randomized phase III trials have demonstrated increased survival in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). The 3 studies included patients with Eastern Cooperative Oncology Group (ECOG) performance status equal to 0–1, with a low level of pain as measured by the Brief Pain Inventory-Short Form scale (BPI-SF) equal to 0–1 (asymptomatic) or 2–3 (minimally symptomatic), respectively. In these trials, metastatic disease was documented. In the IMPACT study [9], sipuleucel-T, an autologous active cellular immunotherapy agent, prolonged OS among men with mCRPC, before or after docetaxel treatment, with a relative reduction of 22% in the risk of death as compared with the placebo group (hazard ratio [HR]: 0.78; 95% confidence interval [CI]: 0.61–0.98; $p = 0.03$). This reduction represented a 4.1 month improvement in median survival (25.8 months vs. 21.7 months). The most common associated adverse events (AEs) were chills (51%), fever (22%), fatigue (16%), nausea (14%) and headache (11%).

In the second study (COU-AA-302) [10], abiraterone, an inhibitor of suprarenal and intratumoral androgen synthesis, in combination with prednisone, was superior to placebo plus prednisone. Overall survival, radiographic PFS and secondary endpoints all favored the abiraterone arm (in terms of time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, PSA progression and decline in performance status). With regard to toxicity, only liver toxicity (grade 3–4 in 8% of patients treated with abiraterone vs. 3% in the control group) and mineralcorticoid effects (i.e. edema, hypertension and hypokalemia) were higher in patients treated with abiraterone. The role of abiraterone in the groups of patients not included in the COU-AA-302 study, especially in patients with symptomatic or visceral metastases, is controversial.

Results of a third study have recently been reported. PREVAIL was a phase III trial comparing enzalutamide activity with placebo in asymptomatic or minimally symptomatic chemotherapy-naïve mCRPC patients [11,12]. Unlike the COU-AA-302 study, only 4% of patients had associated corticosteroid treatment and approximately 12% of them had visceral metastases (lung and/or liver). The study demonstrated a statistically significant benefit in terms of OS and radiographic PFS ($p < 0.0001$ both). Enzalutamide demonstrated benefit with respect to all secondary end points, including the time to initiation of chemotherapy, the time until first skeletal-related event (SRE), complete or partial soft-tissue response, time to PSA progression and rate of decline of at least 50% in PSA. The most common AEs in

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the enzalutamide arm were fatigue, back pain, constipation, arthralgia, and hypertension (7% grade 3–4), and there was one episode of seizures in each treatment arm.

No comparative studies have been conducted with docetaxel against new hormonal treatments. Symptomatic patients were not included in studies carried out in docetaxel-naïve patients, and so docetaxel plus prednisone used in a 3-weekly schedule should be recommended. Patients with minimally symptomatic or asymptomatic mCRPC could be treated with docetaxel especially if some other factors of poor prognosis are present, such as more than two metastatic sites, high Gleason score, PSA level doubling time of less than 55 days, low hemoglobin count, high alkaline phosphatase (ALP) levels and high baseline PSA levels [13,14].

Recommendations:

- None of these treatments has been demonstrated to be useful in CRPC with PSA progression and without metastatic disease.
- Sipuleucel-T will be a treatment option in asymptomatic patients with mCRPC before chemotherapy with docetaxel if regulatory approval is obtained in Europe (level of evidence: Ib; grade of recommendation: A).
- Abiraterone is a treatment option for asymptomatic or minimally symptomatic patients with mCRPC without visceral metastases and previously untreated with chemotherapy (level of evidence: Ib; grade of recommendation: A).
- Enzalutamide will be a treatment option (EU approval expected) for asymptomatic and minimally symptomatic patients with mCRPC, including selected patients with visceral metastases, who have not received previous chemotherapy (level of evidence: Ib; grade of recommendation: A).
- Patients with asymptomatic or minimally symptomatic mCRPC and adverse prognostic factors (presence of visceral metastases) should also be considered for docetaxel treatment (level of evidence: 1a; grade of recommendation: A).

3.1. Progression criteria

In the 3 studies previously described, the time to objective disease progression was established on the basis of radiographic evaluations according to RECIST 1.1, or progression on bone scanning according to criteria adapted from the PCWG2. It is strongly recommended that PSA rise without evidence of confirmed radiographic progression or a SRE should not be used as criteria for starting new systemic oncology treatment, especially during the first 12 weeks of treatment. Clinical criteria recommended for identifying disease progression are a significant increase in the level of pain and analgesic requirements in two consecutive visits, as well as decline in functional status.

Recommendations:

- Patients should be monitored closely, and in the case of radiological or clinical progression should discontinue treatment and be offered other therapeutic alternatives (level of evidence: 1b; grade of recommendation: A).
- Non-responding patients with rapid PSA progression should be considered for treatment discontinuation and be offered chemotherapy (level of evidence: 3; grade of recommendation: C).

4. Symptomatic patient and/or with visceral metastases

4.1. First-line chemotherapy with docetaxel

Cytotoxic chemotherapy with docetaxel is generally advisable for patients with rapid progressive or symptomatic disease for whom less toxic approaches are not an appropriate option. Docetaxel given every 3 weeks in combination with daily prednisone significantly prolonged OS, improved quality of life, pain control, and objective tumor response compared with mitoxantrone plus prednisone in the TAX 327 phase III trial. Based on these results, docetaxel plus prednisone has become the standard initial regimen when chemotherapy is indicated for patients with CRPC [2,15,16].

Recommendations:

- Docetaxel in combination with prednisone is recommended in patients with symptomatic mCRPC or with visceral metastases (level of evidence: Ia; grade of recommendation: A).

4.2. Rechallenge

This strategy was an option for patients who progressed after docetaxel response and who did not experience any severe toxicity. In retrospective studies, docetaxel rechallenge appeared to be associated with more benefit in patients who were retreated after at least 3 months since the last cycle of first-line docetaxel [17,18]. Currently, with the development of new therapies that can delay progression and improve survival, rechallenge with docetaxel could play a role in a small subset of patients and should be reserved until failure has occurred on all of these treatments.

5. Chemotherapy with docetaxel in castration sensitive metastatic prostate cancer (mCSPC)

In the 2014 American Society of Clinical Oncology (ASCO) meeting, results of the CHAARTED study (E3805) were communicated [19]. This study was performed in 790 patients with androgen-sensitive metastatic prostate cancer who were randomized to receive ADT continuously, alone or associated with six cycles of docetaxel chemotherapy at standard doses. Around 65% of patients presented high

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volume of metastases (visceral involvement or more than four bone metastases, with at least one beyond the pelvis and the vertebral column). The primary endpoint of the trial was met with a median OS of 44 months for patients treated with ADT compared with 57.6 months for patients treated with chemotherapy and ADT (HR: 0.61; 0.47–0.80; $p = 0.003$). These differences were even greater in high volume metastatic patients (32.9 months vs. 49.2 months; HR: 0.6; $p = 0.006$), but were not statistically significant in low volume metastatic patients. These results contrast with the GETUG-AFU 15 trial [20], performed with a similar population and treatment, in which no OS differences were found. In the CHAARTED trial, more patients were diagnosed with *de novo* metastatic disease, higher disease volume and worse prognosis than in the GETUG-AFU 15, which could explain the different results. More data are needed to draw definitive conclusions.

Recommendation:

- Awaiting final publications of the CHAARTED trial, six cycles of docetaxel plus ADT can be a therapeutic option for fit patients with hormone-sensitive prostate cancer and high volume of metastases (visceral involvement or more than 4 bone metastases, with at least 1 beyond the pelvis and the vertebral column) (level of evidence: 1b; grade of recommendation: A).

6. Treatment with radium 223

Radium 223 (223Ra) is an alpha particle-emitting radiopharmaceutical that is indicated for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastases. 223Ra has increased both OS and time to first symptomatic SRE in the ALSYMPCA trial. This trial was an international, randomized, double-blind, phase 3 study conducted in men with symptomatic mCRPC comparing 223Ra with placebo [21]. The trial enrolled patients failing on, not eligible for, or refusing prior docetaxel-based chemotherapy (only 57% had received docetaxel).

223Ra significantly improved OS compared with placebo (14.9 months vs. 11.3 months, respectively; HR: 0.70; 95% CI: 0.58–0.83; $p < 0.001$). Time to first SRE was significantly prolonged. The subsequent subgroup analysis reported that survival benefit was similar whether or not patients had received docetaxel (HR: 0.71 vs. 0.74) [22]. Toxicity of any grade showed small differences in the incidence of diarrhea (25% vs. 15%) and thrombocytopenia (12% vs. 6%) [21].

Recommendation:

- 223Ra is a reasonable treatment option in patients with symptomatic bone metastases and without visceral metastases, after docetaxel or in those patients who are not eligible for chemotherapy (level of evidence: Ib; grade of recommendation: A).

7. Treatment with abiraterone, enzalutamide and cabazitaxel after docetaxel

Two molecules have been demonstrated to control the up-regulation of androgen biosynthesis enzymes in two ways. Abiraterone acetate is an inhibitor of the enzyme CYP17 that blocks androgen synthesis in the testis, adrenals and in the tumor itself [23]. On the other hand, enzalutamide inhibits the nuclear translocation of the AR because of its high affinity for AR, its binding to deoxyribonucleic acid (DNA) and its coactivator recruitment [24]. The large phase III trial COU-AA-301 included patients with CRPC progressing after docetaxel with ECOG ≤ 2 [25]. Patients were randomized to receive either abiraterone or placebo plus prednisone. OS increased with abiraterone treatment (15.8 months vs. 11.2 months; HR: 0.74; 95% CI: 0.64–0.86; $p < 0.0001$). Benefits were similar for all secondary endpoints, namely PSA progression, radiologic PFS and PSA response rate. Several grade 3–4 toxicities were more frequent in patients treated with abiraterone, including fluid retention (4% vs. 1%), hypertension (1% vs. 0%) and cardiac disorders (4% vs. 2%).

Enzalutamide has been tested in the phase III AFFIRM trial, where men with CRPC who had received prior docetaxel-based chemotherapy were randomized to either enzalutamide 160 mg or placebo [26]. Steroids use was permitted, but was not a requirement. The primary end point was OS, which was 18.4 months in the enzalutamide group and 13.6 months in the placebo group. Enzalutamide was significantly better than placebo in terms of all secondary endpoints, namely the proportion of patients with PSA level reduction, soft-tissue response rate, quality of life response, the time to PSA progression, radiographic PFS and the time to the first SRE. Treatment was well tolerated. Fatigue, diarrhea and hot flashes rates were higher in the enzalutamide group but were not statistically significantly different from the control group. Seizures were reported in 0.6% of patients receiving enzalutamide. In summary, results obtained with abiraterone and enzalutamide are similar.

Cabazitaxel has demonstrated activity in second-line CRPC [27]. The TROPIC trial showed that OS and PFS were improved with cabazitaxel in patients who had progressed on docetaxel chemotherapy. The authors reported a median OS of 15.1 months in comparison with 12.7 months and a median PFS of 2.8 months in comparison with 1.4 months, respectively. With regard to secondary endpoints, PSA response rate was higher for patients treated with cabazitaxel (39% vs. 18%; $p = 0.0002$), as well as tumor response rate (14% vs. 4%; $p = 0.0005$). The main AEs were hematological toxicity and diarrhea. Recently, updated results at 2 years confirmed the results reported previously [28].

Since 2010, new treatments have been incorporated after first-line chemotherapy. These drugs include chemotherapy, radiopharmaceutical agents such as 223Ra or AR targeted agents such as enzalutamide and abiraterone acetate. The main issue is the decision about which patients will

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benefit most from those treatments. It is difficult to compare data from clinical trials, and there is a lack of studies directly comparing therapies. It is well known that prostate cancer is a heterogeneous disease and different cell populations may co-exist in the same patient. The definition of the subgroups of patients who will achieve more benefit from targeted therapies is an unmet clinical need.

Currently, patients may be classified according to patient condition, tumor characteristics, biochemical aspects or prior treatments. Regarding these prognostic factors [29,30], patients progressing early on docetaxel or presenting with liver metastases, who had short response to first-line hormonotherapy, Gleason score higher than 7, or with high tumor burden, may benefit from chemotherapy treatment with cabazitaxel. However, there is no clear evidence because patients with these characteristics were also included in studies evaluating hormone therapy, in which a benefit was observed.

Recommendations:

- Treatment with cabazitaxel chemotherapy should be considered for patients with mCRPC following progression on docetaxel (level of evidence: Ib; grade of recommendation: A).
- Treatment with abiraterone or enzalutamide should be considered for patients with mCRPC following progression on docetaxel (level of evidence: Ib; grade of recommendation: A).
- After treatment with docetaxel, there are no clearly defined clinical or biological criteria for choosing the next treatment (cabazitaxel, Ra223, abiraterone or enzalutamide).

8. Patients with bone metastases: Bone targeted therapies

Bone metastases occur in more than 80% of patients with advanced prostate cancer. Osteoclast-mediated bone resorption is inhibited by bisphosponates. Zoledronic acid is an intravenous bisphosphonate, which was evaluated in a phase III trial compared with placebo [31,32]. All patients also received supplemental calcium and vitamin D. Results showed that significantly more patients receiving placebo displayed SREs compared with those receiving zoledronic acid 4 mg (44% vs. 33%; difference: −11%; 95% CI: −20% to −2%; $p = 0.021$). Also, significantly fewer patients receiving zoledronic acid 4 mg experienced a fracture (22% vs. 13%; $p = 0.015$). Median time to the first SRE was longer in patients treated with zoledronic acid (488 vs. 321 days; $p = 0.01$). Zoledronic acid requires monitoring for renal function, with dose adjustments (i.e. to keep creatinine clearance at a level between 30 and 60 mL/min) and withholding to prevent renal injury in patients who develop renal impairment during treatment. Treatment with zoledronic acid is not recommended in patients with creatine clearance lower than 30 mL/min.

Receptor Activator of Nuclear Factor Kappa B Ligand (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 trial [33], 1904 patients with CRPC and no previous exposure to intravenous bisphosphonates were randomized to receive 120 mg of subcutaneous denosumab, or 4 mg intravenous zoledronic acid, every four weeks. The use of supplemental calcium and vitamin D were strongly recommended. The median time to first on-study SRE 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 AEs were recorded in a similar proportion in both arms. More events of hypocalcemia occurred in the denosumab group. Osteonecrosis of the jaw occurred infrequently, but more frequently in denosumab-treated patients (22 [2%] vs. 12 [1%]; $p = 0.09$). In both groups, this risk was higher in patients with clinical records of tooth extraction, poor oral hygiene, or use of a dental appliance. Denosumab had no effect on renal function and there is no need for renal monitoring, although it should be noted that in the pivotal trial patients with creatinine clearance lower than 30 mL/min were excluded.

Table 1 summarizes the main phase III trials evaluating agents which have demonstrated activity in patients with mCRPC.

Recommendations:

- Although zoledronic acid, 4 mg intravenously every 3–4 weeks, and denosumab, 120 mg subcutaneously every 4 weeks, are recommended for the treatment of bone metastases in patients with CRPC to prevent bone complications, denosumab has demonstrated superiority over zoledronic acid in a phase III trial (level of evidence: Ib; grade of recommendation: A).
- There are no clear safety data regarding the treatment with these drugs over two years, and thereafter the side effects of these drugs may increase.
- Bone-targeted therapies used as a prevention of SRE should only be administered to patients with castration resistance (level of evidence: Ib; grade of recommendation: A).
- Dental and maxilar examination of patients by a specialist is recommended before the use of these treatments to reduce the risk of osteonecrosis (level of evidence: 3; grade of recommendation: C).

9. Sequential treatment or third-line therapy

As a consequence of the almost simultaneous clinical development of new hormonal agents, the role of these treatments after progression with respect to each other is not yet established. The best therapeutic sequence has not yet been

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Table 1
Phase III trials evaluating agents with demonstrated activity in patients with mCRPC.

Study	*N*	Status	Regimen	rPFS (PFS or tSRE) (months)	*p*	OS (months)	*p*
TAX 327 [2]	1006	CT-naïve	Docetaxel + prednisone vs. mitoxantrone + prednisone	NR	NR	18.9 vs. 16.5; HR: 0.76	0.009
COU-AA-302 [10]	1088	Asymptomatic. CT-naïve	Abiraterone + prednisone vs. placebo + prednisone	NR vs. 8.3; HR: 0.43	<0.0001	NR vs. 27.2; HR: 0.75	0.0097
PREVAIL [11,12]	1717	Asymptomatic. CT-naïve	Enzalutamide vs. placebo	13.8 vs. 3.9; HR: 0.18	<0.0001	32.4 vs. 30.2; HR: 0.70	<0.0001
ALSYMPCA [21]	922	Pre- and post-docetaxel	Radium 223 vs. placebo	15.6 vs. 9.8;HR: 0.66	<0.001	14.9 vs. 11.3; HR: 0.695	0.00007
IMPACT [9]	512	Pre- and post-docetaxel	Sipuleucel T vs. placebo	3.7 vs 3.6;HR: 0.95	NS	25.8 vs. 21.7; HR: 0.78	0.03
TROPIC [27]	755	Post-docetaxel	Cabazitaxel + prednisone vs. mitoxantrone + prednisone	2.8 vs. 1.4;HR: 0.74	<0.0001	15.1 vs. 12.7; HR: 0.70	<0.0001
COU-AA-301 [25]	1195	Post-docetaxel	Abiraterone + prednisone vs. placebo + prednisone	5.6 vs. 3.6; HR: 0.67	<0.001	15.8 vs. 11.2; HR: 0.74	<0.0001
AFFIRM [26]	1199	Post-docetaxel	Enzatulamide vs. placebo	8.3 vs. 2.9; HR: 0.4	<0.001	18.4 vs. 13.6; HR: 0.63	<0.0001
Fizazi et al. [33]	1904	Pre- and post-docetaxel	Denosumab vs. zoledronic acid	20.7 vs. 17.1; HR: 0.82	0.008	19.4 vs. 19.8; HR: 1.03	NS

CT: chemotherapy; HR: hazard ratio; NR: not reported; NS: not statistically significant; OS: overall survival; PFS: progression-free survival; rPFS: radiological progression-free survvial; tSRE: time to skeletal-related event.

defined and there are no molecular or clinical markers to help clinicians to select the best therapy for each patient.

Recently published data suggest that the presence of the variant 7 isoform of AR (ARV-7) in CTCs predicts resistance to abiraterone and enzalutamide. However, these findings need to be prospectively validated [34].

9.1. Sequential treatment

There are limited clinical and preclinical data suggesting the existence of cross-resistance between taxanes and enzalutamide or abiraterone. *In vitro* studies indicate that taxanes may act by disrupting AR signalling. This may represent a potential mechanism for cross-resistance among taxanes and new hormonal agents [35,36]. Published experience on sequential treatment is limited to small retrospective clinical trials.

9.2. Taxanes after abiraterone or enzalutamide

A subset analysis of the Cancer and Leukemia Group B (CALGB) trial 90401 (Alliance) [37], assessed the impact of prior ketoconazole on the benefit achieved in patients with docetaxel therapy and there were no statistically significant differences in terms of OS and PFS.

However, preliminary data suggest a potential decreased benefit of docetaxel in patients who previously received abiraterone acetate. In a retrospective review [38], docetaxel resulted in only 26% PSA response rate, a median time to PSA progression of 4.6 months and median OS of 12.5 months. In another study, 23 patients treated with docetaxel after abiraterone showed a 48% PSA response, with a median OS from the date of the first docetaxel dose of 12.4 months [39].

With regard to cabazitaxel, in a recent publication reporting the outcomes of 59 men with progressing mCRPC treated with cabazitaxel after abiraterone or enzalutamide, PSA and soft tissue response was observed in 39% and 14% of patients, respectively [40]. Median OS and PFS were 15.8 and 4.6 months, respectively. Similarly, in 79 patients treated with third-line cabazitaxel after docetaxel, followed by abiraterone or enzalutamide, a PSA decline of 30%, with a median PFS and OS of 4.4 and 10.9 months, respectively, was observed [41]. In conclusion, cabazitaxel seems to remain clinically active despite prior hormonal manipulations.

9.3. Enzalutamide after abiraterone and/or docetaxel

Retrospective analysis of a small series of patients reported that PSA responses are lower than in second-line studies (13% to 46%) with lower treatment duration, PFS and OS. It is not clear whether abiraterone resistance predicts enzalutamide response [42,43].

9.4. Abiraterone after enzalutamide and docetaxel

Similarly, retrospective analysis of patients who progressed following treatment with docetaxel and enzalutamide has shown modest activity of abiraterone with a PSA response around 8%, and a median time to progression of 15 weeks and time of abiraterone acetate treatment duration of 13 weeks [44].

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Recommendation:

- Overall, based on these limited clinical data, sequential treatment with cabazitaxel, abiraterone and enzalutamide has shown clinical activity and should be considered in patients with mCRPC. The true impact of sequential therapy is not yet established (grade of recommendation: C).

10. Utility of circulating tumor cells as a biomarker in current practice

To date, many platforms have been developed to isolate circulating tumor cells (CTCs), but the CellSearch® system is the only assay approved by the United States Food and Drug Administration (FDA). CTCs in prostate cancer have been shown to be an independent prognostic factor in CRPC in a series of 219 patients with mCRPC, starting a new line of chemotherapy [45]. Baseline CTC counts ≥5/7.5 mL predicted significantly worse results in terms of OS compared with patients with <5/7.5 mL CTCs (11.5 months vs. 21.7 months, $p < 0.0001$). An increase of CTC to ≥5/7.5 mL in patients with initial low counts following treatment has been associated with poor outcomes, whereas a CTC count drop from ≥5/7.5 mL after treatment have been linked to improved outcomes [45,46]. More recently, the pivotal COU-AA-301 study was the first prospective randomized phase III trial to report that an improvement in the CTC count is also associated with improved OS [25].

The use of a low cut-off value (≥5/7.5 mL CTCs) for separating patients into 'favourable' and 'unfavourable' prognostic groups has been examined. An alternative approach is to consider CTCs as a continuous variable [46–48]. Several small studies have also suggested that CTCs could be a promising substitute for tumor tissue biopsies for the assessment of pharmacodynamic markers or for treatment selection in prostate cancer. However, as compelling as some early results may seem, CTCs are associated with several limitations, including the use of non-validated CTC isolation assays [49]. In addition, there are other emerging approaches to the concept of "liquid biopsy", such as whole blood gene expression profiling [50,51], or the genomic profiling of circulating free DNA [52]. Despite CTCs showing great potential as future predictive, pharmacodynamic and/or surrogate biomarkers in CRPC, current evidence limits the use of CTCs for the prognostic stratification of patients.

11. Assessment of elderly patients or patients presenting comorbidities

Prostate cancer is mainly a disease of older men [53]. With the rapid aging of the population, the burden of prostate cancer and the age of patients is likely to increase in the future.

Recently, the International Society of Geriatric Oncology (SIOG) developed recommendations for the assessment and treatment of older men with prostate cancer [54]. After reviewing the literature, the SIOG Prostate Working Group established that G8 screening should be used to determine which patients would get a more accurate geriatric evaluation. A score of 14 or lower indicates impairment requiring geriatric assessment. The most important factors to consider for the evaluation of health status in older men with prostate cancer are comorbidities (measured by the Cumulative Illness Score Rating-Geriatrics), dependence status (measured by activities of daily living [ADL] or instrumental activities of daily living [IADL] scales), and nutritional status (variation of weight during the last 3 months). These tools enable older men with prostate cancer to be classified into one of 3 health status categories: Healthy or Fit, Vulnerable, or Frail.

'Healthy or Fit' older patients are those with a G8 score of more than 8, and they should receive the same standard treatment as younger individuals, which includes standard chemotherapy and hormonal treatments. 'Vulnerable' patients are those with a G8 score of 14 or lower and who are dependent in 1 or 2 ADL, or who present grade 2 comorbidities, or one grade 3 comorbidity, or who are at risk of malnutrition, and who have no neuropsychological problems except depression that may be controlled with medical treatment. Geriatric patients' problems can potentially be reversed through intervention, and patients should receive standard treatment after resolution of any geriatric problem. 'Frail' patients with irreversible impairment are those with a G8 score of 14 or lower, who are dependent in two or more ADL-characterizing irreversible dependencies, who present with several grade 3 comorbidities or one grade 4 condition, or who have severe malnutrition, or abnormal IADL, or neuropsychological problems. Frail patients should receive treatment only depending on their clinical situation [54,55].

In most reported pivotal trials (TAX327, COU-AA-301, AFFIRM, TROPIC), survival benefit is consistent between age groups [16,26,27,56]. Vulnerable and Frail older patients are not usually included in clinical trials as most of them do not fall under inclusion criteria, and hence specially targeted trials are necessary for these populations. The AEs profile of these treatments is good and tolerance is excellent. Thus, no important toxicity problems are expected in aged populations, but information about treatment toxicity focused on Vulnerable and Frail patients is not available in pivotal abiraterone, enzalutamide and 223Ra studies. Nonetheless, in the TROPIC study comparing cabazitaxel and mitoxantrone [27], diarrhea and neutropenia were more frequent in older patients, but toxicity was minimized with dose delays or reductions in the case of important toxicity and with the use of prophylactic granulocyte colony stimulating factor (G-CSF) treatment in patients older than 65 years or with any other risk factor.

223Ra had demonstrated activity and survival benefit in patients not suitable for docetaxel treatment and should be considered as a therapeutic option in older patients, although a geriatric evaluation was not performed in the ALSYMPCA study. Abiraterone or enzalutamide could be a treatment

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option for this population too, but there is no evidence of efficacy in Frail or Vulnerable older patients.

12. Final considerations

Medical oncologists should be aware that management of CRPC has evolved during the last few years from a mainly palliative approach to one based on the availability of modern treatments that may improve OS. These new developments have highlighted the problems that clinicians face when making therapeutic decisions. First of all, scientific advances occur much faster than regulatory approvals. Many new drugs share the same approved indication, but in most cases, there are neither conclusive data on direct comparisons among them, nor on the predictors of response. Moreover, it is quite possible that different timing, sequences or combinations of some of these new agents can further improve survival in patients. Many clinical trials are ongoing, and it is likely that new drugs and/or new indications will be available soon. To complicate things further, CRPC is a very heterogeneous condition, not only in terms of the biology of the disease, but also in the characteristics of patients, i.e. age and comorbidities.

Thus, optimal management of CRPC has become a complex and demanding challenge for medical oncologists. Making decisions concerning the proper selection of the more appropriate treatment for our patients with CRPC requires a full understanding of the disease. To begin with, it is important to be aware of the situations requiring rapid therapeutic management, such as poorly controlled pain, hypercalcemia, pericardial effusion, disseminated intravascular coagulation or spinal cord compression. A comprehensive assessment of the disease and the patient should then be carried out, including current metastatic status, dose and duration of prior therapies, comorbidities, and geriatric evaluation [55,57].

Before choosing the appropriate treatment, the oncologist has to design a global strategy considering all the available present and future treatment options for a particular patient, including the possibility of participating in clinical trials. Once the therapeutic decision has been made, it is also necessary to make a careful follow-up of toxicities, considering criteria for dose adjustment, as well as an adequate evaluation of response and progression criteria. Additionally, CRPC is usually a symptomatic disease, and other palliative measures such as radiotherapy need to be kept in mind. Finally, it is important to note that, as in other areas of oncology and particularly in the rapidly evolving field of prostate cancer, the best management of patients with CRPC requires interdisciplinary collaboration between medical oncologists, urologists and radiotherapists. Regular clinical meetings to discuss the best therapeutic alternatives, specific training within each specialty, and an adequate infrastructure to ensure the optimal administration of therapies, as well as the management of complications, are strongly recommended.

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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Biography

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