Chapter 7
Castration-Resistant Prostate Cancer: Mechanisms, Targets and Treatment

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Prostate cancer is the most common malignancy in men, and remains the second leading cause of cancer-related death in this gender [1]. Data suggests that 10–20% of patients with prostate cancer metastasis develop castration-resistant prostate cancer (CRPC) within 5 years of follow-up, and that the median survival since development of castration resistance is approximately 14 months (range 9–30) [2]. Additionally, patients with non-metastatic CRPC are at higher risk of disease progression. Approximately 15–33% of patients develop metastasis within 2 years, increasing the mortality burden in this population [3, 4].

Treatment of metastatic CRPC (mCRPC) is palliative, and disease evolution is often associated with significant morbidity. Before 2010, docetaxel chemotherapy was the only treatment showing a survival advantage, which translated in its approval by the US Food and Drug Administration (FDA), and in its widespread use as first-line therapy globally [5, 6]. More recently, however, several large randomized clinical trials have led to the approval of new agents for the treatment mCRPC. New therapies have all demonstrated an overall survival (OS) benefit in patients with mCRPC who progressed after docetaxel therapy [7]. Also the new generation hormonal manipulations—abiraterone and enzalutamide—have shown an OS benefit in asymptomatic or minimally symptomatic patients who had not received prior chemotherapy [8].

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Therapeutic strategies with a symptomatic purpose, such as external radiotherapy, chemotherapy with mitoxantrone or radioisotopes such as samario-153, may also be used. Additionally, the use of bone metabolism-modifying agents, such as denosumab or zoledronate, has shown efficacy in the prevention of skeletal complications in this setting.

7.1 Castration-Resistance

The mainstay of treatment for metastatic hormone-sensitive prostate cancer is androgen deprivation therapy (ADT), aiming at the suppression of circulating testosterone. The goal of ADT is to decrease circulating testosterone to "castrate levels," corresponding to a serum measurement lower than 50 ng/dL. The decline of testosterone to castrate levels results in a decrease in cancer cell proliferation, with subsequent induction of apoptosis. Despite the anti-proliferative response to ADT, cancer cells eventually become resistant to therapy, and signs and/or symptoms of progression are observed in most patients [9, 10]. "Castration resistant" designation is applied to prostate cancer when a measurable progression of disease is observed at the castrate level, detected either by a sequential rise in prostate specific antigen (PSA), or by imaging findings (computed tomography, magnetic resonance imaging, or radionuclide bone scintigraphy). The "castration resistant" designation is privileged over the previously used designations of "androgen independent" and "hormone refractory" disease because, despite absence of circulating testosterone, the tumor remains functionally dependent on androgens and on the androgen receptor [10, 11].

7.2 Treatment of mCRPC

7.2.1 Next Generation Hormonal Therapies

Initial treatment of metastatic prostate cancer consists of androgenic depletion by orchidectomy or luteinizing hormone releasing hormone (LHRH) agonists/antagonists, which may be associated with antiandrogens. Due to the tumor hormonal dependency, LHRH axis blockade should be maintained *ad eternum* in mCRPC, as observed in the SWOG 9346 study.

Testosterone and dihydrotestosterone are the major agonists of the androgen receptor. Leydig cells produce approximately 97% of circulating testosterone, which is converted into dihydrotestosterone in prostate by the 5-alpha-reductase enzyme, the remaining being synthesized in the adrenal gland. When pharmacological or surgical castration is performed, dihydrotestosterone may still be detected in tumor tissues at sufficiently high levels to activate the androgen receptor. Regardless of

where it is generated, conversion of dihydrotestosterone precursor through CYP17A1 expression-dependent enzymatic reactions will always be necessary. This was the rational underlying the development of potent CYP17A1 inhibitors [12].

Between 2011 and 2012, new hormonal therapies (abiraterone and enzalutamide) emerged as approved treatments for mCRPC.

Abiraterone is a derivative of pregnenolone, which prevents androgen biosynthesis by inhibiting CYP17A1 at the gonad and extra-gonadal levels and in tumor tissues, leading to an effective androgen depletion [12]. In 2011, the COU-AA-301 Phase 3 study, including 1195 symptomatic mCRPC patients previously treated with docetaxel, compared abiraterone 1000 mg (once daily [qd]) plus prednisone 5 mg (twice daily [bid]) with placebo plus prednisone 5 mg (bid). The study showed an increase in progression-free survival (PFS) (5.6 months vs 3.6 months, $p < 0.001$) and OS (15.8 months vs. 11.2 months, HR = 0.65, $p < 0.001$) with abiraterone [1]. A sub-analysis of the COU-AA-301 study investigated pain control in symptomatic patients post-docetaxel chemotherapy. Results showed that patients in the abiraterone acetate plus prednisone arm experienced more palliation (45% vs 28.8%; $p < 0.001$) and faster median time to palliation of pain (5.6 vs 13.7 months; $p = 0.002$) than those in the placebo arm [13, 14].

Enzalutamide is an androgen receptor inhibitor that blocks several steps of the androgen receptor signaling pathway. It has a high affinity for the ligand domain of the androgen receptor (approximately 5–8 times higher than bicalutamide). The AFFIRM study, in 2012, included 1199 symptomatic mCRPC patients previously treated with taxanes, and compared enzalutamide 160 mg (qd) with placebo. This study found a PFS and OS benefit (8.3 months vs 2.9 months, HR 0.40, $p < 0.001$; 18.4 months vs. 13.6 months, HR 0.63, $p < 0.001$, respectively) associated with enzalutamide (Table 7.1) [15].

More recently, Phase 3 studies evaluated these agents as first-line treatment of asymptomatic or minimally symptomatic mCRPC patients prior to chemotherapy. In 2013, the COU-AA-302 study randomized 1088 patients with no visceral disease to treatment with abiraterone 1000 mg (qd) plus prednisone 5 mg (bid) or placebo plus prednisone 5 mg (bid). Treatment with abiraterone translated in an advantage of PFS (16.5 months vs 8.3 months, HR 0.53, $p < 0.001$) and OS (34.7 months vs 30 days, HR 0.80, $p = 0.0027$) [16]. In 2014, the PREVAIL study recruited 1717

Table 7.1 Efficacy of abiraterone and enzalutamide in the second-line treatment of mCRPC

	Overall survival		
COU-AA-301	Median (months)	Hazard ratio (IC 95%)	p
Abiraterone 1000 mg/dia + prednisolone 5 mg *per os bid*	15.8	0.74 (0.64–0.86)	<0.0001
Placebo + prednisolone 5 mg *per os bid*	11.2		
AFFIRM			
Enzalutamide 160 mg/dia	18.4	0.63 (0.53–0.75)	<0.0001
Placebo	13.6		

Table 7.2 Efficacy of abiraterone and enzalutamide in the first-line treatment of mCRPC

	Overall Survival		
COU-AA-302	Median (months)	Hazard Ratio(IC 95%)	P
Abiraterone 1000 mg/dia + prednisolone 5 mg *per os bid*	34.7	0.81 (0.70–0.93)	0.0033
Placebo + prednisolone 5 mg *per os bid*	30.3		
PREVAIL			
Enzalutamide 160 mg/dia	35.3	0.77 (0.67–0.88)	0.0002
Placebo	31.3		

patients, including those with visceral metastasis, to receive enzalutamide 160 mg or placebo once daily. An OS benefit (35.3 months vs 31.3 months, HR 0.71, $p < 0.001$) was observed in the enzalutamide arm (Table 7.2) [17].

Both abiraterone and enzalutamide are currently approved for the first-line treatment of asymptomatic or minimally symptomatic mCPRC patients, and for the second-line treatment of symptomatic mCPRC patients who failed docetaxel.

These agents are better tolerated than cytostatic therapy. Due to inhibition of CYP17A, abiraterone suppresses the production of androgens and cortisol, with an increase of ACTH. This results in the production of mineralocorticoids, with associated side effects. Hypertension, fluid retention and hypokalaemia are the most common adverse events, although a slight increase in transaminases and a very small percentage of grade 3–4 side effects can also be observed. Supplementation with 5 mg of prednisone (bid) is, therefore, recommended.

Enzalutamide is also a well-tolerated drug. In the AFFIRM and PREVAIL trials, adverse events observed in both study arms consisted of fatigue, diarrhea and facial flushing. As a risk of seizures was reported for some patients in both trials (five out of 800 patients in the AFFIRM trial, and one out of 1717 patients in the PREVAIL trial), a risk/benefit evaluation should be made before starting therapy in patients with a prior history of epilepsy. Although hepatotoxicity has been described as an adverse effect of other antiandrogens, it was not observed in the AFFIRM or PREVAIL trials. The glucocorticoid receptor has been postulated as responsible for enzalutamide resistance in the presence of androgen receptor inhibition, due to overlap with the androgen receptor at various DNA binding sites and to rescue of gene transcription expression previously inhibited by enzalutamide [18]. Therefore, it is recommended that glucocorticoids are discontinued when starting enzalutamide, since there is no need for replacement therapy.

In either indication, therapy should be maintained until disease progression, with the first recommended imaging evaluation performed at 12 weeks, and a total PSA determination performed every month. Progression is assumed:

1. In presence of bone scan with ≥2 lesions, 12 or more weeks after initiation of therapy, confirmed according to PCWG2;
2. in second-line, post-docetaxel therapy of symptomatic patients, when in presence of at least three:

(a) Progression of total PSA 25% above baseline, with a minimum increase of 5.0 ng/mL;
(b) Radiographic progression defined by one of the following:

Bone scan with ≥2 lesions not due to flare effect, confirmed according to PCWG2;
Radiographic evidence of progression of lesions assessed by modified RECIST criteria;

3. clinical or symptomatic progression defined by one of the following:

(a) pain worsening in two consecutive evaluations (>30% increase in bone or visual pain scales or >30% increase with opioid use);
(b) bone events (pathological fracture, spinal cord compression, surgery or radiation to the bone);
(c) need to increase prednisone dose or to switch to a more potent glucocorticoid to treat cancer-related symptoms.

7.2.2 Chemotherapy

The use of cytostatic agents in mCPRC began in the 1990s with the use of mitoxantrone. A randomized Phase 3 study compared mitoxantrone plus corticosteroids to corticosteroids alone, showing a benefit of treatment with mitoxantrone in the control of pain and improvement in quality of life, but not in OS. This paradigm was maintained until 2004, when accumulating evidences supported the use of docetaxel. At this time, two Phase 3 clinical trials were published, establishing the OS benefit associated with the use of docetaxel: the SWOG 99-16 and TAX-327 trials [19, 20].

SWOG 99-16 compared docetaxel 60 mg/m^2 (D2) plus estramustine 280 mg (three times a day [tid];D1–D5) with mitoxantrone 12 mg/m^2 (D1) plus prednisone 5 mg (bid) given every 3 weeks (q3w) in 770 patients with mCPRC. The study evidenced a statistically significant increase in OS in the docetaxel plus estramustine arm (17.5 months vs 15.6 months, HR 0.8 p = 0.01) [19]. TAX-327 compared two dosages of docetaxel (30 mg/m^2 EV weekly for 5 weeks in 6 week cycles and 75 mg/m^2 given q3w plus prednisone 5 mg bid with mitoxantrone 12 mg/m^2 q3w plus prednisone 5 mg bid in 1006 patients with mCRPC. Median OS was 18.9 months in the docetaxel q3w arm, 17.4 months in the docetaxel weekly arm and 16.5 months in the mitoxantrone arm, with only the first group showing a statistically significant advantage (HR 0.79 p = 0.004) [20]. This study led to the approval of docetaxel 75 mg/m^2 q3w plus prednisone 5 mg bid as first-line treatment of mCPRC, due to toxic effects and lack of additional efficacy of the estramustine combination (Table 7.3).

Because TAX-327 and SWOG 99-16 trials allowed a maximum number of 10 and 12 treatment cycles, respectively, the benefit of additional treatment cycles was investigated in a retrospective analysis by *Pond G. et al.* This analysis included the patient populations of the TAX-327 and the CS-205 trial treatment arms, which compared the administration of docetaxel 75 mg/m^2 q3w plus prednisone 5 mg bid plus

Table 7.3 Docetaxel efficacy data in mCRPC

	Overall survival		
TAX 327	Median (months)	Hazard ratio (IC 95%)	P
Docetaxel 75 mg/m^2, D1 + prednisolone 5 mg *per os bid* (q3w)	18.9	0.79 (0.67–0.93)	0.004
Docetaxel 75 mg/m^2 D1 semanal, D1, w1–5 + prednisolone 5 mg *per os bid* (q6w)	17.3	0.86 (0.74–1.02)	0.086
Mitoxantrone 12 mg/m^2 + prednisolone 5 mg *per os bid* (q3w)	16.5		
SWOG 99-16			
Docetaxel 60 mg/m^2, D2 + Estramustine 280 mg per os, D1-D5 (q3w)	17.5	0.8 (0.67–0.97)	0.02
Mitoxantrone 12 mg/m^2 + prednisolone 5 mg *per os bid* (q3w)	15.6		

AT-101 with docetaxel 75 mg/m^2 q3w plus prednisolone 5 mg bid plus placebo. Although patients completed 17 treatment cycles, there was no survival advantage in completing more than ten consecutive cycles of treatment [21].

According to a study by *Kume H. et al.*, intermittent docetaxel therapy was shown to be feasible in selected patients, based on response assessment. According to the study protocol, therapy should be discontinued if total PSA levels drop below 4 ng/mL, with at least 50% reduction over the target level at treatment start, and should be restarted if total PSA levels rise above over 2 ng/ml, with at least 50% increase over the nadir. Among 51 patients included in the study, 27 (52.9%) were eligible for intermittent therapy. The median interval without therapy was 266 days for the first interruption, and 129.5 days for the second interruption. An OS benefit was observed in the intermittent therapy group (HR 2.98, p = 0.023), probably reflecting a subgroup of patients with a more indolent-, better prognosis-disease, amenable to benefit from this strategy and from its reduced cumulative toxicity [22]. Similar results were observed in a retrospective analysis of the ASCENT trial where, with a similar protocol, PSA response rates higher than 50% were observed in 45.5% of patients after a median of 126 days without therapy [23]. In a recent retrospective analysis by *Oudard S. et al.*, favorable responses to docetaxel therapy were observed (total PSA decrease>50%). Furthermore, retreatment with docetaxel was possible, with no marked difference in OS (18.2 months vs. 16.8 months, p = 0.35) compared to other non-taxane-based therapies, and a progression-free interval longer than 6 months was predictive of better response [24].

For patients with comorbidities, where docetaxel at a 75 mg/m^2 q3w dose is expected to lead to therapy postponement or discontinuation due to toxicity, the 50 mg/m^2 every 2 weeks (q2w) regimen may be an option. A reduction in grade 3–4 adverse events, including neutropenia and febrile neutropenia, was observed with the q2w regimen, without compromising efficacy: time to progression was 5.6 months vs 4.9 months (p = 0.014), and OS was 19.5 months vs 17.0 months (p = 0.021) in favor of the q2w regimen [25].

The most recent data on the role of chemotherapy in metastatic prostate cancer came from the CHAARTED and STAMPEDE studies. These two trials suggest an earlier use of docetaxel chemotherapy in castration-sensitive disease, along with hormone therapy, with an important OS advantage in patients with a high-volume disease (visceral disease and/or ≥4 bone lesions). It is, therefore, extremely important to consider an early therapy start in this setting.

Recommendations for treatment with docetaxel are as follows:

- To complete a minimum of six cycles, up to a maximum of ten, if justified by evidence of clinical benefit; perform imaging evaluation until cycle 4 in case of sustained biochemical progression;
- in patients with a total PSA drop below 4 ng/mL and a reduction ≥50% of target level at treatment start, treatment interruption can be considered. In this case, treatment should be resumed if total PSA levels rise above 2 ng/ml, with an increase of at least 50% of the nadir;
- maintaining docetaxel treatment after an initial response with total PSA > 50%, and stable disease with a ≥ 6-month progression-free interval without chemotherapy, can be an option for selected patients not eligible for other, more effective, therapies;
- in patients with significant comorbidities, the 50 mg/m^2 every 2-week docetaxel schedule can be an option, retaining efficacy with lower toxicity.

In 2010, the new taxane cabazitaxel was approved for the treatment of mCPRC in patients previously treated with docetaxel. This drug was found to retain antitumor activity when used in P-glycoprotein-overexpressed cell lines and in those with tubulin mutations, partially responsible for resistance to docetaxel [26].

A phase 3 study (TROPIC) compared cabazitaxel 25 mg/m^2 (EV administered q3w) plus prednisone 5 mg (bid) with mitoxantrone 12 mg/m^2 (EV administered q3w) in 755 patients with mCRPC that had been previously treated with docetaxel chemotherapy. Results showed an OS advantage with cabazitaxel (15.1 months vs 12.7 months, HR 0.70, $p < 0.0001$), evidencing its benefit in the second-line chemotherapy setting [27]. The use of cabazitaxel is currently reserved for symptomatic patients following docetaxel therapy, and neutropenia prophylaxis with granulocyte stimulation factors should be considered. Standard dosage and setting for cabazitaxel was further evaluated in the FIRSTANA and PROSELICA trials. There was no survival advantage in using cabazitaxel in first-line and the 20 mg/m^2 dosage was

Table 7.4 Cabazitaxel efficacy data in the treatment of mCRPC

	Overall survival		
TROPIC	Median (months)	Hazard ratio (IC 95%)	P
Cabazitaxel 25 mg/m^2 D1 + prednisolone 5 mg *per os bid* (q3w)	15.1	0.70 (0.59–0.83)	<0.0001
Mitoxantrone 12 mg/m^2 + prednisolone 5 mg *per os bid* (q3w)	12.7		

Table 7.5 Taxane-related adverse effects in the treatment of mCRPC

TAX 327		TROPIC	
Adverse event	Frequency (%)	Adverse event	Frequency (%)
Alopecia	65	Neutropenia G3/G4	82
Fatigue	53	Diarrhea	47
Nausea/emesis	42	Fatigue	37
Neutropenia G3/G4	32	Nausea	34
Diarrhea	32	Emesis	23
Onycholysis	30	Asthenia	20
Peripheral neuropathy	30	Constipation	20
Stomatitis	20	Hematuria	17
Peripheral edema	19	Abdominal pain	12
Dysgeusia	18	Dyspnea	12
Anorexia	17	Fever	12
Dyspnea	15	Arthralgia	11
Myalgia	14	Anemia G3/G4	11
Tearing	10	Febrile neutropenia	8
Epistaxis	6	Thrombocytopenia G3/G4	4
Anemia G3/G4	5		
Febrile neutropenia	3		
Thrombocytopenia G3/G4	1		

equivalent to the 25 mg/m^2 dosage, both in first and second line, with a better toxicity profile (Tables 7.4 and 7.5) [28, 29].

7.2.3 Sipuleucel-T

Sipuleucel-T is an immunotherapeutic agent consisting of activated antigen-presenting cells derived from patient's peripheral mononuclear cells (PBMCs), which are subsequently stimulated *in vivo* with a recombinant fusion protein (prostatic antigen, prostatic acid phosphatase and granulocyte stimulating factors), and reinfused into the patient. This agent has been evaluated in several randomized clinical trials. Although none of these trials showed a PFS benefit, a statistically significant OS benefit was observed. The largest trial was the Phase 3 IMPACT study, published in 2010, which demonstrated an OS increase (25.8 months vs 21.7 months, HR 0.78, p = 0.03) compared to placebo in patients with bone or lymph node metastasis and a chemotherapy-free interval ≥3 months. This trial included a highly selected patient population: more than 80% of patients had no previous cytostatic therapy, 75% of patients had a Gleason score ≤7, 53% of patients had no pain complaints, and 43% had low-bone and bone-only disease [30].

Sipuleucel-T has been recently approved by the European Medicines Agency (EMA) for the treatment of mCRPC. However, the procedure requirements, absence of predictive biomarkers of response and associated costs may limit its use.

7.2.4 Radionuclide Therapy: Radium-223

Radium-223 is an α-emitting, bone-seeking calcium mimetic that selectively targets and binds to areas of increased bone turnover in bone metastasis. The drug is administered by intravenous injection at 4-week intervals, up to a total of six injections. The ALSYMPCA trial was a randomized, double blind, Phase 3 study comparing six injections of radium-223 with placebo in men with CRPC and bone-only metastasis who received, were not eligible to receive, or declined docetaxel chemotherapy [31]. Median OS was longer with radium-223 than with placebo (14.9 vs 11.3 months; hazard ratio 0.70, 0.58–0.83; $P < 0.001$). Subsequent subgroup analysis showed a survival benefit with radium-223, irrespective of previous docetaxel use [32]. In addition, a significant improvement in median time to first symptomatic skeletal event was observed for radium-223 compared to placebo (15.6 vs 9.8 months; hazard ratio 0.66, 0.52–0.83; $P < 0.001$). Radium-223 was well tolerated and associated with fewer adverse events than placebo. Although the difference was not statistically significant, a higher rate of diarrhea (25% vs 15%) was seen with radium therapy. Other known side effects include nausea, vomiting, peripheral edema, and hematologic abnormalities (anemia, leukopenia, thrombocytopenia, neutropenia). Radium therapy was also associated with a meaningful improvement in quality of life [31].

7.3 How to Choose the First-Line Therapy

Approved molecules with survival benefit in mCRPC			
Mechanism of action	Molecule	Trial	Survival advantage, months
Androgen receptor	Enzalutamide	AFFIRM (post-docetaxel)	18.4 vs 13.6
		PREVAIL (pre-docetaxel)	35.3 vs 31.3
Androgen synthesis inhibition	Abiraterone	COU-AA-301 (post-docetaxel)	15.8 vs 11.2
		COU-AA-302 (pre-docetaxel)	34.7 vs 31.3
Citotoxicity—Microtubule stabilization	Docetaxel	TAX-327 (first-line)	19.2 vs 16.3
	Cabazitaxel	TROPIC (post-docetaxel)	15.1 vs 12.7
Radionuclide—Calcium mimetic	Radium-223	ALSYMPCA (pre/post docetaxel)	14.9 vs 11.3

The choice of first-line therapy and the therapeutic sequencing are not straightforward, due to the number of available therapies and the absence of randomized clinical trials evaluating their sequence. In 2015, a consensus meeting was held for the first time. It was called the St Gallen Advanced Prostate Cancer Consensus Conference—APCCC 2015, and gathered investigators from leading clinical trials and opinion leaders in an effort to answer key clinical questions. Based on the resulting document and in evidences available in the literature, a therapeutic algorithm is proposed.

According to this algorithm, mCPRC patients are initially assigned to one of two groups: eligible or non-eligible for docetaxel cytostatic therapy.

7.4 Patients Non-eligible for Docetaxel Therapy

The following criteria apply for considering a patient ineligible for docetaxel therapy:

- ECOG Performance status (PS) of 3, and most patients with ECOG PS of 2;
- inadequate bone marrow reserve (absolute neutrophil count <1500 cells/mm^3 or platelet count <100,000 cells/mm^3);
- inadequate organ reserve (total bilirubin increase ≥1.5×; AST/ALT>3.5 times the upper limit of normal);
- patient refusal to receive chemotherapy.

Although docetaxel use is not contraindicated in elderly patients, caution should be taken when administering the drug in the geriatric population, due to non-prostate cancer-related comorbidities. This evaluation and decision should be made for each patient individually. These patients can be candidates for new-generation hormonal therapy, although trials demonstrating their benefit (COU-AA-302 and PREVAIL) have not been performed on the geriatric population, and no information exists regarding their risk/benefit ratio or quality of life in this setting.

7.5 Patients Eligible for Docetaxel Therapy

Patients eligible for chemotherapy require a previous evaluation for presence or absence of symptoms, disease site and preexisting adverse prognostic factors.

7.5.1 *Definition of Asymptomatic/Minimally Symptomatic Patients*

The benefit of docetaxel therapy in this patient population may be questionable, considering the drug's toxicity and the potentially absent symptomatic relief, since patients already are asymptomatic or minimally symptomatic. Nevertheless, there is not an unequivocal choice between chemotherapy and new hormonal manipulations, as there are a fraction of patients who are primarily resistant to the latter. The splicing variant of the androgen receptor, AR-V7, was studied by *Antonarakis et al.*, and it seemed to have conferred resistance to both abiraterone and enzalutamide patients [33, 34]. That effect was not seen in taxane treated patients, with the splicing variant emerging as possible biomarker. This concept has been recently validated by *Howard Scher et al.* and could have an important role in the first-line therapy selection for mCRPC patients [35, 36].

There is no evidence of superiority of abiraterone compared to enzalutamide or vice versa, and the use of these drugs should be evaluated in each patient individually, considering the most favorable toxicity profile. Sipuleucel-T can be used in this indication concomitantly with other therapies.

The definition of "minimally symptomatic patient" is not clear in the PCWG2 criteria, but by analyzing inclusion and exclusion criteria in these trials a definition can be reached:

- the COU-AA-302 trial only included patients with an ECOG PS of 0 or 1, and measured symptomatology by the Brief Pain Inventory—Short Form (BPI-SF) score. Patients with a score of 0 or 1 were considered asymptomatic, while those with a score of 2 or 3, minimally symptomatic. Patients with visceral disease were excluded;
- the PREVAIL trial included patients with ECOG 0–2, BPI-SF score <4, no opioid therapy, and visceral disease;
- the IMPACT trial excluded patients with ECOG>2, visceral disease, and bone events (bone fractures, spinal cord compression or radiation therapy/bone surgery). This trial only included asymptomatic patients at the beginning, and subsequently also the inclusion of symptomatic patients (the criteria for this population was not detailed);

Considering this, an asymptomatic or minimally symptomatic population can be characterized as having:

- an ECOG PS of 0–1;
- pain defined according to BPI-SF scale of 0–1 (asymptomatic) or 2–3 (minimally symptomatic), with no need for opioid therapy;
- no previous bone events (long bone-fracture, spinal cord compression or bone radiation therapy/surgery).

7.5.2 Disease Site

Presence of visceral disease in mCRPC is rare, and associated with worse prognosis. According to Phase 3 trials performed in the first-line setting of mCRPC treatment, only TAX-327, SWOG 99-16 and PREVAIL (12% of patients) included patients with visceral disease. Therefore, recommendations on the use of docetaxel or enzalutamide in this subpopulation should be made based on available evidences.

Hepatic metastasis (versus other visceral metastatic sites) are associated with worse prognosis, as observed in the subanalysis of the AFFIRM study and in a subanalysis performed by *Halabi et al.* in the TAX-327 study [37]. Consequently, although a benefit was observed in patients with visceral metastasis treated with enzalutamide in the PREVAIL study, hepatic metastasis should be considered a factor of poor prognosis, and first-line docetaxel therapy, recommended [38].

7.5.3 Adverse Prognostic Factors

Adverse prognostic factors represent a significant risk for rapidly progressive disease, and should be addressed in the asymptomatic or minimally symptomatic population before a treatment decision between docetaxel or new generation hormonal manipulations be made.

A Gleason score >8 in local disease (pre-radiotherapy or surgery) represents a poor prognosis factor for the development of metastasis and mortality. The same is true for a twofold increase in total PSA time in non-metastatic biochemical recurrence. The latter has also been validated as an adverse risk factor in the metastatic setting, but there was no definite cut-off value; in the TAX-327 study, a PSA doubling time value higher than 55 days was established as prognostic for survival [39].

Time to castration resistance, defined as the time from nadir of total PSA under androgen deprivation until confirmed biochemical progression, is a poor prognostic factor and can also be predictive of response to future hormonal manipulations. It does not seem to have an impact on the PSA response to docetaxel or cabazitaxel [40, 41].

Tumor burden should be considered, evaluating the type of metastization (lymph nodes, bone, lymph nodes and bone, visceral). The prognostic implications of this parameter were highlighted in the CHAARTED and STAMPEDE studies, where docetaxel was associated with a survival improvement in patients with hormone-sensitive disease and high tumor burden (defined as four or more bone lesions and/or visceral disease) [42, 43].

When considering a predominantly bone-metastizing disease, bone involvement is translated in bone turnover and lysis parameter alterations, including alkaline

phosphatase. In the TAX-327 study, an alkaline phosphatase elevation above the median value was a poor prognostic factor, as it was in the COU-AA-302 study [16]. LDH elevation is a tumor lysis marker, frequently associated with tumor burden. In the COU-AA-302 study, elevation of this parameter was a poor prognostic factor for survival [44]. A low pre-treatment hemoglobin value may reflect spinal cord involvement due to neoplastic infiltration, related to more advanced disease. Also a ratio higher rate of lymphocytes/neutrophils in peripheral blood prior to therapy is, not only a poor prognostic marker, but also an indicator of worse response to either docetaxel or abiraterone.

The final analysis of the COU-AA-301 and COU-AA-302 trials showed that anemia, alkaline phosphatase elevation, ECOG, time from hormone therapy to other therapy and presence of visceral metastases were poor prognostic factors of survival, and presence of four to six of these parameters in the same patient translated into a global survival lower to 6 months [14, 16].

In presence of such adverse prognostic factors, earlier onset of chemotherapy should be considered instead of new generation hormone manipulations. The reason for this is the risk for rapid progression, which can cause the deterioration of patient's overall status and the potential loss for docetaxel therapeutic window.

7.6 Subsequent Therapies

Data from small cohort retrospective studies suggests that clinical activity of docetaxel following abiraterone acetate and enzalutamide is reduced (with response rates lower than those reported in the TAX-327 trial), and that cabazitaxel activity is maintained (with response rates similar to those observed in the TROPIC study). Based on this data alone, there is currently no sufficiently robust information to determine the best sequence of available drugs for first-line treatment.

Sequencing of the two hormonal manipulations agents also seems to have a low efficacy. Several small retrospective series reported lower response rates and median PFS for the use of abiraterone post-enzalutamide and vice versa, compared with trials in the second-line setting (COU-AA-301 and AFFIRM), although higher PSA response rates were observed with the use of enzalutamide in the second line [18].

In absence of robust evidences concerning the sequencing of different agents, all hypothesis are possible for the referred indications. For a patient treated with docetaxel in first line who is clinically asymptomatic/minimally symptomatic and has no poor prognostic factors, docetaxel re-challenge (using the criteria previously described: total PSA response >50% and range free of disease for more than 6 months without therapy) or, preferably, switch to a secondary hormonal manipulation can be considered. If patient is symptomatic or progressing under docetaxel, cabazitaxel therapy should be given. In case of bone-only metastasis patients, use of

radium 223 should be considered (currently only indicated in patients who have had at least two previous lines).

For patients who experienced secondary hormonal manipulations, subsequent treatment with docetaxel should be considered, followed by cabazitaxel or radium 223 (for bone-only metastasis patients). Sequential therapy with another secondary hormone-manipulating agent should be left for salvage therapy in highly selected patients who had an excellent prior response to the first therapy.

7.7 Future Perspectives

Defects in homologous repair deficient (HRD) genes, such as BRCA 1/2, ATM, PALB2, RAD51, FANC and CHEK2 are present in about 1/5–1/4 of mCRPC patients [45]. Activity has been seen with poly adenosine disphosphate-ribose polymerase (PARP) inhibitors in the TOPARP trial [46] and to some extent platinum therapy [47].

PTEN loss is also common in mCRPC, activating AKT signalling [45]. Targeting this pathway has shown significant activity in a phase 2 trial and is now being tested in a phase 3 setting [48, 49].

Germline mutations in mismatch-repair genes (MLH1, MSH2, MSH6 and PMS2) are described in a small percentage (0.6%) of men with mCRPC, but recently an hypermutated phenotype was describe by *Pritchard et al.* in mCRPC, with mismatch repair deficiency reaching 12% of mCRPC patients [50]. Pembrolizumab, a monoclonal antibody targeting programmed death 1 (PD-1), was approved by the Food and Drug Administraion (FDA) for cancers with defective mismatch repair [51]. In unselected patients resistant to enzalutamide this agent has considerable activity, warranting further investigation, specially in patients with defective mismatch repair [52].

Prostate specific membrane antigen (PSMA) is highly expressed in mCRPC. PSMA-ligands can be coupled to radionuclides, such as actinium or lutecium (alfa and beta particles, respectively). These molecules were already tested in phase II trials in a heavily treated population, with promising results [53, 54]. A recombinant T-cell engaging bispecific monoclonal antibody (BiTE) directed against PSMA and the CD3 epsilon subunit of the T cell receptor complex, can have potential immunostimulating and antineoplastic activities and is currently being tested [55].

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