Expert opinion on first-line therapy in the treatment of castration-resistant prostate cancer

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A B S T R A C T
Treatment of metastatic castration-resistant prostate cancer (mCRPC) has been revolutionized in recent years. It is well known that androgen receptor is still active in most patients with disease progression and serum testosterone levels <50 ng/dL. Moreover, further hormonal maneuvers, either through decreasing androgen levels (abiraterone) or by targeting the androgen receptor (AR) pathway (enzalutamide), prolong survival. In addition, a new cytostatic able to overcome docetaxel resistance, cabazitaxel, and the radioisotope radium 223 have been incorporated to the armamentarium of mCRPC.

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mCRPC is not only a heterogeneous tumor, it changes over time developing neuroendocrine features or selection of clones resistant to hormonal maneuvers. In addition, the multiplicity of current treatments, make it necessary to design algorithms that help the specialist to choose the most appropriate treatment for a particular patient. The lack of randomized trials comparing face to face the different available options limit the scope of this review. In this article, the authors describe the prognostic factors for first line therapy in patients with mCRPC, and propose a treatment algorithm for mCRPC based on the levels of scientific evidence available and, if not available, on the consensus between medical professionals. Finally, the panel discuss how to define progressive disease in the setting of mCRPC and treatment with targeted therapies.

1. Introduction

The management of metastatic castration-resistant prostate cancer (mCRPC) has undergone a radical change in recent years with the development of new therapies targeting AR--abiraterone (AA) and enzalutamide (ENZ)—a new taxane able to overcome docetaxel--cabazitaxel (CBZ)--and a radiosiotope, radium 223. They have all shown to prolong overall survival (OS) in patients with mCRPC progressing after docetaxel-based chemotherapy [1–4]. In addition, AA and ENZ have also achieved OS benefits in chemo-naïve minimally symptomatic patients, in which only one immunotherapy—sipuleucel-T—had previously done so [5–7]. Still, 10 to 20% of patients are primarily refractory to either AA or ENZ [5,6]. Adequate characterization of those patients would avoid undesirable delays of potentially more successful therapies.

In 2004, the combination of docetaxel and prednisone was first able to demonstrate a survival benefit in mCRPC patients and it is considered the standard of care (SOC) [8,9], although there is no a clear consensus for the optimum timing to be initiated [10–13]. Besides docetaxel, in first line therapy, physicians in charge of patients with mCRPC have available three treatments for which there is strong evidence of survival as well as QoL benefit, with a favorable benefit-risk profile: AA, ENZ, and radium 223 (for patients with predominantly bone metastases). Because of this, the classification of pre-docetaxel and post-docetaxel setting is old fashion nowadays. Guidelines should contemplate therapy with a first line therapy, either docetaxel, radium-223, AA or ENZ, and subsequent second and third-line therapies. Discussion with the patient and into multidisciplinary teams about the best therapy for patients progressing under castrate levels of testosterone is imperative, incorporating a more modern classification between asymptomantic and symptomatic patients [14].

In order to perform clinical trials in more homogeneous groups of patients, the Prostate Cancer Trials Working Group (PCWG2) established 5 clinical subgroups ranging from a patient with local progression (subtype 1) to a metastatic patient with visceral involvement (subtype 5) [15]. The PCWG2 recognizes the absence or presence of symptoms as a prognostic factor, but not as a stage of progression of the disease itself [15]. The classification’s final aim is to define patient groups in which treatment intervention should have low toxicity—because of excellent prognosis and asymptomatic disease—or groups where a higher level of toxicity could be acceptable due to symptomatic disease and poor prognosis. The pivotal studies of AA and ENZ in chemo-naïve patients included asymptomatic patients where a low toxicity profile seems a prerequisite to establish a new therapy [5,6]. Otherwise, a new concept emerges from the ALSYMPCA study, where radium 223 was compared to placebo in symptomatic patients with only or predominantly bone metastases that had received chemotherapy, refused chemotherapy or were considered “not suitable for chemotherapy”, a term that should be better defined [4].

The importance of including chemotherapy in the management of mCRPC despite the number of new therapeutic options is enhanced after the publication of the results from the CHAARTED—ECOG 3805 study, wherein patients with high tumor burden, early introduction of docetaxel still in the hormone-sensitive disease setting, provided a benefit in survival. In this trial, patients defined as with high tumor burden (defined by present of visceral metastases, or presence of extra-axial bone metastases) receiving docetaxel plus androgen deprivation therapy had a median survival of 48.2 months vs 32.2 in patients receiving only androgen deprivation therapy. Although a similar trial previously published was negative, the GETUG trial, there are subtle differences between the CHAARTED and GETUG trials in terms of trial design and patient population recruited that may lead to different clinical outcomes, including the CHAARTED trial patients with far advanced disease [16,17].

A third trial, STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy), have communicated evidence of the benefit in terms of overall survival of adding docetaxel in the hormone-sensitive setting for patients either with advanced locoregional or metastatic disease [18]. Since 2005, more than 6500 men with prostate cancer were recruited making STAMPEDE the largest randomized study to date. The addition of new therapies as well as a change in the standard of care for this growing cancer population can be expected from this study that is still ongoing in the UK.

Four were the therapies analyzed in the study and 2962 the hormone-naïve prostate cancer patients assigned to either of the following groups: SOC with androgen deprivation therapy for at least three years and radiation therapy for eligible patients; SOC with six cycles of docetaxel; SOC with zoledronic acid for two years; and SOC with both docetaxel and zoledronic acid. The addition of zoledronic acid to hormonal therapy, either alone or with docetaxel, did not improve survival in comparison to SOC with docetaxel alone. On the other hand, the addition of docetaxel showed an improvement in survival from 43 months to 65 months in men with detectable metastatic disease (61% of the 2962 men included in the analysis). The overall survival in the docetaxel arm (after a median follow-up of 42 months) was 77 months (24% improvement) in comparison to 67 months of the standard of care arm. The time to relapse of the docetaxel arm also showed an increase by 38% in all the patients.

These results will lead to a change in the current metastatic prostate cancer therapy towards the early introduction of docetaxel to patients with hormone sensitive disease. Moreover, the meaning of these results may also influence the management of hormone-refractory disease since the benefit of the early introduction of chemotherapy surpasses the benefit of chemotherapy in more advanced disease.

The objective of the panel when elaborating this guideline was to help define the optimum first-line therapy for each individual patient. As there is no randomized information, this objective can

only be reached through a rigorous review of the available evidence and through the consensus of the specialists involved in mCRPC management. Medical oncologists and urologists have collaborated in the elaboration of the present manuscript. Finally, definition of progressive disease as well as a short review of modern predictive molecular factors are included.

2. Classification of patients for first-line therapy

Patients with CRPC can be included into two groups: those eligible and those ineligible for docetaxel chemotherapy. Patients ineligible for chemotherapy might follow hormonal therapy (although there is no information of the risk/benefit ratio or quality of life in this population from specifically designed clinical trials) or radioisotopes if they had predominantly bone metastatic disease and are symptomatic. Patients eligible for chemotherapy are classified according to the presence or absence of symptoms. In addition, a special consideration is made for patients with visceral metastases.

2.1. Definition of patients ineligible for docetaxel treatment: UNFIT patients

Docetaxel-based chemotherapy has a number of contraindications. Absolute contraindications may include poor general condition (ECOG 3 and most ECOG 2 patients), poor bone marrow reserve (baseline neutrophil count <1500/mm^3), hypersensitivity to the active substance or any of its excipients and poor organ function (serum bilirubin > normal range and/or SGOT y SGPT values >3.5 times the upper limit of the normal range) [19]. Relative contraindications—with a recommendation of special precaution of use—include age-related comorbidities not related to prostate cancer, and persisting frailty after an appropriate geriatric assessment according to the International Society of Geriatric Oncology (SIGO) criteria since the adverse events of chemotherapy may be exacerbated in such patients [19,20]. Finally, patients may refuse chemotherapy. These patients could have been included in the ALSYMPCA trial if they were symptomatic and had predominantly bone disease [4].

2.2. Definition of asymptomatic or minimally symptomatic patients

The pivotal trial for docetaxel, TAX327, included both symptomatic and asymptomatic patients. However, in a time when there were no other therapeutic options, treatment with docetaxel was delayed in most of the patients until symptoms developed. In addition, it is well known that the presence of symptoms, specifically pain, is an adverse prognostic factor in mCRPC [21–23]. The definition of minimally symptomatic patients according to the PCWG2 is intended to identify patients in whom the benefit of docetaxel treatment can be doubtful or not cost-effective, considering its associated toxicity [15]. There is no a single standard definition of minimally symptomatic patients. As this group of patients has been the object of different randomized trials in the last few years, to build a definition of minimally symptomatic patients, the panel considered the inclusion and exclusion criteria in these trials.

The IMPACT trial (sipuleucel-T vs placebo) initially included asymptomatic patients with a Gleason score ≤ 7, although subsequently allowed the inclusion of patients with any Gleason score and mild symptoms [7]. Patients with a performance status (PS) >2, visceral metastases, bone events (long bone fractures, spinal cord compression, prior radiotherapy or surgery) or who had received more than 2 previous lines of chemotherapy were excluded; therefore, this was not a first-line treatment only trial [7].

The COU-AA-302 trial (AA plus prednisone vs. placebo plus prednisone) recruited patients with an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, and with no or minimal symptoms as assessed by the score of the Brief Pain Inventory–Short Form (BPI-SF) [5,24]. Patients were considered asymptomatic if they had a score of 0 or 1, and minimally symptomatic if they had a score of 2 or 3 on any of the questions [5]. The PREVAIL trial (ENZ vs placebo) recruited patients with Karnofsky index ≥ 70% who did not require opioids or steroids for symptom control and who had not previously received palliative radiotherapy [26]. Finally, sipuleucel was compared to placebo in patients with PS 0-1 not requiring opioids [27]. The criteria from the different trials used to define minimally symptomatic disease are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1 Criteria to define asymptomatic or minimally symptomatic patients with mCRPC [5–7,22–25].</th>
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<tbody>
<tr>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>PS 0-1 or Karnofsky index &gt; 70%</td>
</tr>
<tr>
<td>No pain or pain does not interfere with daily activities of patient and does not require treatment with opioids</td>
</tr>
<tr>
<td>No skeleton-related event during the castration-resistance period</td>
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<tr>
<td>No need for corticosteroid therapy to control symptoms</td>
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2.3. Risk factors for a rapid symptomatic progression in patients with minimally symptomatic disease

Factors of poor prognosis and subsequent risk of rapid disease progression are classified as histological (Gleason score), biochemical (absolute prostate specific antigen (PSA) level, PSA doubling time (PSA-DT), hemoglobin (Hb), alkaline phosphatase (AP), albumin, lactate dehydrogenase (LDH), neutrophil/lymphocyte ratio (NLR) and testosterone levels), and clinical factors (radiological progression-free survival (rPFS) and type of progression) [1].

2.3.1. Gleason score

In the setting of localized disease, Gleason score is one of the criteria included in the D’Amico risk classification [28]. A Gleason score > 8 has been related to an unfavorable course for the development of metastases and mortality in cohorts of patients previously undergoing radical prostatectomy and/or radiotherapy [28,29]. For advanced disease, a post-hoc analysis of patients included in the TAX327 trial showed a benefit in survival for those patients receiving docetaxel with a Gleason score ≥ 7 (HR 0.69, 95% CI 0.52–0.91; p = 0.009) [30]. These data support those previously reported in a model used to predict the probability of OS in patients with mCRPC [22]. The prognostic value of the Gleason scale is, nevertheless, limited by itself due to the fact that tumors with Gleason score < 7 are almost never represented in randomized trials. In addition, we do not know what the appropriate cut-off point is. In patients treated with AA as first or second-line, the Gleason score was not a predictor of response either in first-line or second-line therapy.

2.3.2. Absolute PSA level and PSA doubling time

In the non-metastatic biochemical failure setting in patients that underwent radical prostatectomy, PSA-DT is a predictor of survival [31]. As stratified by different cut-off points (<3.0 vs. 3.0–8.9 vs. 9.0–14.9 vs. ≥15 months), a PSA-DT value <3 months was associated with mortality attributable to prostate cancer (HR 54.90,
95% CI 16.70-180) [32]. In mCRPC, a short PSA-DT constituted a poor-risk factor for survival (HR 0.79; p < 0.0001) [33]. Nevertheless, there is not an established cut-off point for PSA-DT. One study showed that a PSA-DT ≤ 70 days (HR 1.79; p < 0.0001) was significantly associated with a shorter survival time than a PSA-DT > 70 days, whereas another study reported mean survival times of 16.5 and 26.4 months for patients with a PSA-DT < 45 and ≥ 45 days respectively [34,35]. The TAX 327 study set a cut-off point PSA-DT value > 55 days as the prognostic value for survival [23].

The absolute PSA level has prognostic value in patients with mCRPC both in the pre-chemotherapy and post-chemotherapy setting, but it is less consistent than PSA-DT. Two placebo-controlled studies of atrasentan and zolendronate for prevention of bone metastases showed that absolute PSA levels ranging from 10 and 13 ng/ml were associated with a shorter time to occurrence of the first bone metastases; however, PSA-DT was a better predictor of survival [36,37]. A retrospective analysis of the denosumab trial on prevention of bone metastases showed that the maximum benefit in metastasis prevention was achieved in high-risk patients, defined by a short PSA-DT [38]. Nonetheless, the update of the Halabi nomogram only included the absolute value of PSA and not PSA-DT [39].

2.3.3. Hemoglobin, alkaline phosphatase, and lactate dehydrogenase

Anemia is a well-known adverse prognostic factor in both symptomatic and asymptomatic mCRPC [22,40]. A subanalysis of patients treated with docetaxel provided further support for this finding (HR 1.11, CI 1.03-1.19; p = 0.004) [22]. Bone metastases in mCRPC are characterized by an imbalance between osteogenesis and osteolysis [41]. AP levels are associated with bone disease and are a predictor of survival in patients with mCRPC [33,42]. Thereby, in the TAX327 study, AP elevation above the median was an adverse predictor of survival (HR 1.27; CI 1.15-1.39; p < 0.0001) [23]. In the same way, the COU-AA-302 study showed mean survival times of 23.6 and 27.5 months for AP values below and above the mean respectively [5]. In a post-hoc analysis of COU-AA-302, high AP and PSA above the third quartile at baseline and during treatment represented an added risk of adverse clinical outcomes in chemo-naive patients [43]. In patients treated with radium 223, AP normalization was a favorable factor for survival [44].

LDH is a marker of tumor burden. Both LDH and circulating tumor cells (CTC) were prognostic factors for survival in the COU-AA-302 trial, patients with LDH levels higher than the median value had poorer OS [45]. In a study for development and validation of a model for predicting OS in patients with mCRPC, LDH was identified as an OS predictor (HR 1.37; 95% CI 1.21-1.55; p < 0.001) [22]. These data were supported by a subsequent study on 1296 patients treated with chemotherapy [46]. Any of these factors individually define a poor prognosis for a specific patient or predict the results of a therapy, while coexistence of some of them define clearly a group of patients with poor prognosis. Final analyses of the COU-AA-301 showed anemia, plus elevation of AP, ECOG, albumin, time from initiation of hormone-therapy to AA and presence of visceral metastases as prognostic factors for survival, considering as poor prognosis the coexistence of four to six of these factors in the same patient, showing this subgroup of patients an OS of less than six months [1]. These factors have also been validated in the pre-docetaxel setting [47].

2.3.4. Neutrophil/lymphocyte ratio

The NLR has been found to be prognostic in many solid tumors, with high NLR associated with worse OS and higher recurrence rates [48]. The biological basis of this remains unclear, but is likely related to altered tumor-inflammatory cell interactions. In men with mCRPC treated with AA, NLR ≥ 5 was associated with lower PSA response rates and shorter survival [49].

2.3.5. Tumor burden

A high tumor burden, evaluated as limited to bone vs bone plus lymph nodes or visceral metastases, combined with NLR and LDH levels, was prognostic of survival in patients with mCRPC receiving AA [49]. The prognostic and therapeutic implications of tumor burden were proved with the communication of the results from the CHAARTED study, where docetaxel improved survival in patients with a high tumor burden in the setting of hormone sensitive metastatic disease [16].

2.3.6. Testosterone levels

Serum testosterone levels, although under castration, are a prognostic factor for survival. Testosterone escapes in the course of treatment with hormone blockade are associated with poorer survival [50]. A small Japanese study of patients progressing on a LHRR agonist suggests that serum testosterone level is a predictor of survival and response to bicalutamide rescue therapy [51]. A retrospective analysis of patients with mCRPC enrolled into different chemotherapy clinical trials suggested better survival in patients with testosterone even at the highest castration level [51]. A correlation has also been suggested between the probability of response to salvage hormonal therapy and testosterone level. Univariate analyses of androgen levels (testosterone and adrenal) by Ryan et al. was prognostic of survival in patients receiving AA or placebo, although it was not preserved in the multivariate analyses and was not predictive of response to therapy [52]. Gomez de Liaño et al. analyzed the prognostic value of testosterone levels in patients going to first-line chemotherapy [53]. Survival was significantly better for patients with testosterone levels above median [53]. In addition, preliminary data suggest that testosterone levels were predictive of response to second-line hormonal maneuvers [53]. Post-hoc analyses of TAX327 also showed testosterone level as prognostic of survival, but they were not predictive of the efficacy of docetaxel [54].

2.3.7. Radiological progression-free survival

Biochemical progression is a prelude to radiological progression, being diagnosed in some trials after a median of 5.7 months [55]. As a consequence, radiological progression is a further step in advanced disease. In fact, rPFS is one of the prognostic factors proposed by the PCWG2 [15,46,56]. Analyses based on patients enrolled into the TAX 327 trial suggest that the type of progression has an impact on OS (HR 1.37 for measurable disease progression and 1.29 for bone progression measured by bone scan, p = 0.005 and 0.01, respectively) [23,56].

2.3.8. Poor response to prior hormone therapy

The quality of the response to prior hormone therapy can be estimated by the time to PSA nadir, absolute PSA nadir value and time to castration resistance. Time to PSA nadir more or less than 7 months is a predictive factor for survival in patients with metastatic hormone sensitive prostate cancer treated with androgen deprivation therapy [57]. Failure to achieve an absolute nadir value below 4 ng/ml at 6 months is associated with younger age, higher prestudy PSA, worse performance status, weight change, bone pain, higher Gleason score (≥ 8), presence of visceral metastases, and distant lymphadenopathy [58]. Finally, time to castration resistance is a prognostic factor of survival, and it may constitute a
predictive factor of response to further hormonal maneuvers. In patients submitted to second-line hormonal maneuvers with AA, ketoconazole-hydrocortisone, diethylstilbestrol, and bicalutamide in five clinical trials, time to castration progression (≥ 16 vs <16 months) significantly predicted the biochemical response rate (58% vs 18%) and the progression-free period (5 vs 3 months) [59]. Unfortunately, there is not a clear cut point. It has been published ranging from 12 months to 24 months [60,61]. In the post-docetaxel study comparing ENZ with placebo, duration of prior hormone therapy was a predictor of survival [2]. Time to initiation of AA shorter than 36 months was one of the prognostic factors included in the nomogram predictive of survival or the COU-AA-301 [1].

On the other hand, time to castration resistance does not appear to affect PSA response with docetaxel or cabazitaxel [60].

2.3.9. Prior ketoconazole therapy

The only study in which sensitivity to AA was analyzed in patients who had received ketoconazole was a phase I trial on 33 patients with mCRPC who had not received chemotherapy, of whom 19 (58%) had previously been treated with ketoconazole [60]. In this study, a >50% reduction in serum PSA was evaluated as a treatment response criterion [62]. The results, without providing a high level of evidence, showed that prior treatment with ketoconazole in the pre-docetaxel phase should not be an exclusion criterion for treatment with AA, but did suggest a lower efficacy of the drug in chemo-naive patients [62].

2.4. Symptomatic patients

In patients with symptoms clearly secondary to the disease, such as pain from bone metastases (even if it has been controlled with palliative radiotherapy), lower limb edema (due to growth of pelvic or retroperitoneal lymphadenopathies), presence of visceral metastases (even if asymptomatic), or impaired general condition due to disease progression, chemotherapy with docetaxel continues to be the standard treatment because it has shown a clear benefit in OS of these patients as compared to mitoxantrone [8,9].

2.5. Patients with visceral metastases

Visceral metastases are uncommon in prostate cancer, but they are associated to a poor disease course [63]. They are included as an adverse prognostic factor in both the Halabi and Armstrong nomograms and in the two pivotal trials of docetaxel [22–24]. In post-docetaxel randomized studies with CBZ, AA and ENZ, approximately 25% of patients recruited had visceral metastases [1–3]. In all three studies, presence of visceral metastases was only a prognostic, not predictive factor of response [1–3].

In the scenario of patients with pre-docetaxel mCRPC, no data are available about use of AA in patients with visceral metastases. In the COU-AA-302 study, comparing AA to placebo, presence of symptoms or visceral involvement were exclusion criteria due to the risk of rapid progression [5,64]. On the other hand, 12% of patients included in the PREVAIL trial had visceral metastases (lung and/or liver) [65]. Treatment with ENZ still provided a benefit compared to placebo (HR 0.69 and 0.82) [65]. The presence of visceral metastases was an inclusion criterion in the CHARTED study, where patients still with hormone-sensitive disease benefit in disease survival from docetaxel [16].

Within visceral metastases, hepatic metastases appear to be specifically correlated with a poorer prognosis. In the randomized trial of docetaxel and prednisone plus bevacizumab or placebo on 1050 patients with mCRPC, 5.6% had hepatic metastases. Although presence of these metastases was not significantly associated with poorer results in the biochemical remission rate or time to progres.ion, poorer overall survival was reported (22 vs 14.4 months; p < 0.019) [66]. In the subanalysis of patients with visceral metastases in the AFFIRM study, the presence of hepatic metastases resulted in lower median survival as compared to pulmonary metastases (9.0 vs 16.5 months in the ENZ arm and 5.7 vs 10.4 months in the placebo arm) [67].

According to the above, the presence of significant visceral or hepatic metastases is associated with shorter survival in mCRPC. Taking into account that it is a factor of poor prognosis and the scarcity of data on the first-line hormonal approach, treatment with docetaxel seems recommendable in this group of patients [12]. An update of the data from TAX327 by Halabi, et al., showed that hepatic metastases were the most adverse prognostic for survival among the visceral ones [39]. In patients with visceral metastases in other locations, the decision should be individualized based on the presence of other characteristics of the disease (Gleason, PSA-DT or tumor volume) (Table 2).

2.6. Molecular biomarkers

In patients with mCRPC, the number of CTC constitutes a dynamic biomarker. Baseline CTC are prognostic of OS while the reduction in the number of circulating cells is a surrogate marker of response to therapy [68,69]; it is accepted that fewer than 50 CTC is a good prognosis parameter, and it probably should be considered for stratification in clinical trials. Although FDA has approved its use as a biomarker, the results of ongoing analyses to finally state the predictive value of early changes in therapy according to number of circulating cells are still pending. The results of the Olimos study add to the data already existing on the expression of microRNA profiles capable of defining prognostic groups [70]. Recently, the androgen receptor splice variant AR-V7, has been associated to resistance to ENZ and AA in men with mCRPC [71]. No patient with this splice variant, showed response to either salvage maneuver [71]. On the other hand, responses to docetaxel or cabazitaxel do not seem to be affected by the presence of AR-V7, supporting chemotherapy as the first-line option for these patients expressing AR-V7 [72].

Automated quantitative determination of bone metastases using the bone scan index may have diagnostic, prognostic and predictive value in patients with mCRPC, but it is still subject to validation [73]. Markers of tumor activity in bone as N-telopeptide and bone AP (reflecting osteolytic and osteoblastic activity) have been shown to be prognostic and survival markers [74–77].

Still, there is not one single factor predictive of response either to hormonal maneuvers or chemotherapy. Different prognostic factors are well established. In nomograms, the combination of those factors define subgroups of patients with poor prognosis and risk of rapidly growing disease that might benefit from more aggressive first or second-line therapies. In addition, data coming from the “West Coast Dream Team” suggest the importance of re-biopsy to define therapy. Analyses of 124 biopsies in patients resistant to AA or ENZ found 13% of patients with small cell carcinoma, and additional 28% with an intermediate-type carcinoma [78]. These findings have prognostic value and they can have therapeutic implications.

3. Cross-resistance between abiraterone and docetaxel and between abiraterone and enzalutamide

The data available on sequencing of AA, ENZ, and docetaxel are even more limited, and no definitive conclusion applicable to clinical practice may therefore be drawn at this time. In a retrospective analysis conducted on 35 patients who had received AA in phase II studies before receiving docetaxel, patients who had not reduced their PSA levels by more than 50% were seen to be refractory to docetaxel, and only 26% had a biochemical response [53]. Time to PSA...
progression was 4.6 months, and OS was 12.5 months [79]. These results, clearly inferior to those observed in the pivotal docetaxel trials, could suggest the existence of cross resistance between AA and docetaxel or simply a more advanced stage of the disease.

On the other hand, the few retrospective studies conducted of treatment with ENZ after AA and vice versa also suggest a worse efficacy of these drugs as compared to when they are used in patients without prior second-line treatment [65,80–83]. CBZ might not have a cross-resistance effect as a result of its dual mechanism of action, which is less dependent on the androgen receptor [84,85].

4. When to finalize first-line therapy?

Historically, post-treatment changes in PSA have not demonstrated robust associations with survival and not qualified as an endpoint to support regulatory approval. In addition, the limited degree of nodal and visceral disease in mCRPC has reduced the utility of standard imaging outcome measures, which also fail to accurately assess bone disease, the most common site of spread. As mentioned above, PCWG2 defined radiological criteria for progressive disease considering patients with either RECIST evaluable disease or bone only disease. PCWG2 emphasized the need to maintain men on effective therapies and reduce this misclassification of progression, and these guidelines were incorporated into nearly every phase II and III trial in CRPC since their development. Radiological progression-free survival was a surrogate marker of overall survival in the COU-AA-302 trial [86]. Patients and investigators accepted these designs and also accepted that early signs of progression (for example, increasing PSA) did not necessarily represent the end of treatment benefit. On the other hand, avoiding exposure to expensive and also ineffective drugs is mandatory, especially when there are available potential salvage therapies that may prolong life. The orteronel trial shows that this rule for stopping therapy is adequate, and that salvage therapy avoided any benefit in survival for orteronel compared to placebo but it implies that salvage therapy should be delivered at the right time. Confirmed symptomatic disease due to tumor progression should lead to a salvage therapy. Shortening of PSA-DT might advance a salvage therapy.

CCT have been considered a possible surrogate marker. Data from the cabozantinib trial rise doubts: despite a benefit in terms of response in number of CCT, no differences in survival were observed between patients receiving orteronel and those receiving placebo. When several effective therapies are available in clinical practice, as for mCRPC, multiple parameters should be considered in public health decisions as long as the novel agents display favorable safety profiles.

5. Discussion and algorithm

The panel tried to summarize the previous data in an algorithm. First, dividing patients into fit or unfit for docetaxel, then
in symptomatic vs asymptomatic or minimally symptomatic. An adequate definition of asymptomatic or minimally symptomatic patients would identify patients with mCRPC at low risk of rapid progression and, therefore, candidates for a treatment with a low toxicity profile. As there is no randomized trials, this definition can only be established by consensus. Some characteristics that define these patients are summarized in Table 1. In clear opposition, it would be the symptomatic patient, at risk of rapid progression, and in need for the right choice of therapy and rapid response, for whom docetaxel is the treatment of choice, as those patients have not been included in randomized trials and no drug or combination of drugs has been superior to docetaxel in a randomized trial. In the modern scenario, the introduction of new effective therapies in chemo-naive patients, although great news for patients, include in itself a risk that some patients may not receive docetaxel therapy at all because their performance status has deteriorated too rapidly through an unsuccessful treatment by AR-targeted agents. Therefore, evidence may support that the choice of first-line treatment may have therapeutic implications as well as the delay to salvage therapy for a patient already progressing [87].

Castration-resistant disease has classically been defined, relative to treatment with docetaxel, as pre- and post-docetaxel. The definition of a patient in a pre- and post-docetaxel situation, which is purely artificial, will gradually be replaced by others, such as a patient resistant or not to treatment at AR-targeted agents, as new definitions of the concept of hormone resistance are incorporated. For example, the NCCN guidelines, 2015 version, classify patients for a first-line therapy with docetaxel and patients for a first-line therapy with AR targeted therapies. With the incorporation of at least four new effective therapies for castration-resistant patients, both pre- and post-docetaxel (ENZ, AA, radium 223 and CBZ), the argument to delay docetaxel administration to reserve the only effective therapy available disappears. In any case, the availability of effective therapies in mCRPC with different mechanisms of action requires to discriminate, by means of clinical or biological markers, the most adequate sequence of therapies for a specific patient, in order to optimize the risk-benefit ratio and to avoid undesirable cross resistance phenomena as a potential consequence of starting an inadequate treatment.

Pending validation of genetic footprints that correctly classify patients, we do not currently have predictors of response to a hormonal or cytostatic treatment. However, we do have prognostic factors which, when taken together, as reflected in numerous nomograms, allow for defining a population of patients with poor prognosis and, therefore, at risk of rapid development of symptoms derived from the disease. Grouping different prognostic factors permits to increase the accuracy of prognostic classifications [88]. The algorithm proposed by the panel in Fig. 1, in which different prognostic factors are added, defines minimally symptomatic disease and patients not eligible for treatment with docetaxel, and may help us with decision-making in patients with mCRPC.

Authors contribution

Dr. Maroto: Honoraria from Astellas, Bayer and Janssen. Participation in clinical trials involving cabazitaxel and enzalutamide.

Dr. Arranz: Participation in clinical trials involving cabazitaxel and abiraterone.

Dr. Gallardo: Honoraria from Sanofi and Janssen. Participation in clinical trials involving cabazitaxel, abiraterone and enzalutamide.

Dr. Climent: Honoraria from Sanofi, Janssen, Bayer and Astellas. Participation in clinical trials involving cabazitaxel and abiraterone.

Dr. Alcaraz: Advisory and speaker from Sanofi, Janssen, Astellas and GSK.

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References


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