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Grey Zone

## Metastatic Castration-resistant Prostate Cancer: Major Progress Leading to Even More Questions

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### Article info

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In metastatic patients, androgen suppression can induce long-term remission. The development of castration-resistant disease is constant, usually after a median 11 mo, leading to metastatic castration-resistant prostate cancer status (mCRPC). Docetaxel (Doc) has been the standard of care for mCRPC since 2004. Nowadays, two second-line hormonal treatments (SLHT; abiraterone acetate [AA] and enzalutamide [E]), another taxane (cabazitaxel [Cab]) a vaccine (sipuleucel T), and a bone-targeted agent (radium 223) have been shown to increase survival. After years of ineffective treatment, we are facing more questions with major practical impact. The treatment choice in the 2016 European Association of Urology-European Society for Radiotherapy and Oncology-International Society of Geriatric Oncology prostate cancer guidelines [1], based on available information, has a low level of evidence.

### 1. When to start second-line treatment?

For mCRPC patients, we are still using suboptimal imaging modalities such as bone and computed tomography scan. More sensitive exams such as whole-body magnetic

resonance imaging (MRI) or specific positron emission tomography tracers such as choline or prostate-specific membrane antigen are available. This might lead to the reclassification of patients as metastatic but currently considered as being M0. This would lead to an earlier and prolonged use of salvage drugs for a still unproven survival benefit.

In 2016, classical second-line hormonal manipulations have no place. None have been associated with more than a prostate-specific antigen (PSA) response, while life-prolonging drugs are available. Outside the patient's wishes there is no rational to wait once the mCRPC status is characterized. Apart from a highly unlikely randomized control trial, data from PREVAIL and COU-302 clearly suggest a decreased survival with a waiting attitude; despite receiving more second-line treatment in the control arm, the survival benefit is only obtained with the early use of active drugs.

### 2. How to choose the first line?

This is still unclear. There are two main questions. How to choose between SLHT, chemotherapy, or alternative

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compounds (radium 223 or sipuleucel T)? If SLHT is considered how to choose between AA and E?

SLHT is the most often used treatment in mCRPC patients. But a *systematic* attitude is suboptimal with up to 30% primary SLHT resistance. An early individualization would avoid unnecessary ineffective and expensive treatment, and the delay of active drugs.

Metastatic CRPC is a heterogeneous situation with a median survival of 27 mo for M1a, 20 mo for M1b, and only 12 mo with liver metastases. Pain and anemia are also prognostic factors while predictive factors for SLHT efficacy are needed but are still lacking. The initial duration of castration efficacy is considered to be predictive. The optimal threshold for a *no-go* decision remains unclear; the shorter the more reliable (less than 6 mo), but a formal consensus is still lacking [2]. Bone marrow biopsy is currently the best available clinical tool. These results from a single center and a small group of patients deserve a formal large comparison. The need for an aggressive biopsy might represent a practical limitation even if confirmed.

The suggestion of not giving SLHT to patients with visceral metastases must be revisited. These localizations are associated with a poor prognosis and represent up to 18–20% of mCRPC. Postponing an active treatment would be a waste of time, with the risk of a lost treatment opportunity. SLHT is effective after Doc for visceral metastases. The rationale that these drugs would be ineffective before Doc is unclear. This efficacy has been suggested in a small subgroup with E, while data for AA are lacking. Multiple visceral metastases, lytic bone lesions, low PSA with extended disease, initial response to castration of less than 6 mo, or a small cell or neuroendocrine histology suggest *anaplastic lesions*. Upfront chemotherapy, eventually using a platinum salt has been suggested as a better option compared with SLHT in these very poor prognosis situations.

Biology should soon lead to predictive factors. Androgen receptor splice variant-7 is suggested to be a key driver for SLHT resistance. Although this has been confirmed [3], the initial simple finding must be somewhat reconsidered as responses have been observed in androgen receptor splice variant-7 patients [4]. Inherited DNA repair defects, present in up to 11% in M1 patients [5], might be associated with a clear benefit for targeted treatments using poly-adenosine diphosphate ribose polymerase inhibitors. This could represent the first individualized treatment in mCRPC, a policy often used in lung or breast cancers for years.

No formal comparison exists between AA and E, and such a trial is highly unlikely. Besides absolute contraindications, the choice is based on side effects, associated comorbidities, and potential drug-drug interaction. If chemotherapy is the first option, Doc remains the standard. Results from FIRSTANA [6] might question this attitude: Cab and Doc lead to the same survival, while the best safety profile is observed with Cab 20 mg/m<sup>2</sup>.

The optimal place for radium 223 remains unclear. There is a strong rationale for combination with other systemic agents provided an acceptable toxicity and improved outcome. The real place of vaccine is even more tricky.

Sipuleucel T is the only Food and Drug Administration/European Medicines Agency-approved vaccine, leading to a significant survival benefit compared with placebo in mCRPC [7]. But logistical and financial constraints represent major limitations for its use. Other vaccines are being tested in mCRPC such as DCVAC (dendritic cells stimulated by killed LNCaP cells) or ProstVac (poxvirus-based vaccine). The real position of vaccines in the treatment journey is even more difficult as data from sipuleucel T and from ProstVac suggest a better survival benefit for less advanced situations. This might be related to a decreased immune system in more advanced situations. Finally, vaccines might be used in combination with immune checkpoints inhibitors (such as cytotoxic T-lymphocyte associated protein 4/programmed cell death protein 1-programmed death-ligand 1 inhibitors), as immunogenic intensifiers [8]. This *immune avenue* that opened with sipuleucel T might soon become a key treatment player, possibly at an earlier stage.

### 3. How to define progression/response evaluation?

The key for follow-up is the overall clinical response, especially the symptom improvement. However, this is not enough as an early confirmed progression might lead to an early treatment change, allowing for multiple subsequent regimens.

Thoraco-abdominal computed tomography scan and bone scan are mandatory to check for progression, without clear interval. The general rules of Response Evaluation Criteria In Solid Tumors-1.1 criteria apply for visceral metastases, while bone lesions size are never considered. The use of whole body MRI, although more sensitive, leads to major uncertainty. Discordant responses are observed especially in bone, with associated growing and decreasing lesions size, while the bone scan remains stable. These findings have never been considered and as yet bone progression is defined with the occurrence of two new lesions later confirmed on a bone scan. The use of MRI might change the monitoring, provided clear rules are available.

Opposed to all the previous situations, treatments should not be stopped for PSA progression alone. In case of significant clinical progression very likely related to disease, treatment should be changed, even without PSA or radiographic progression. The same would apply for unequivocal visceral disease progression without clinical deterioration or PSA progression. The role of biopsy, based on the castration-induced small-cell histology is unclear. Where to biopsy and dealing with the results are key unanswered questions.

At progression the need to stop SLHT at treatment switch must be formally analyzed. Androgen-driven clones might still exist and might be reactivated when stopping SLHT.

### 4. Secondary progression: sequencing

A cross-resistance exists between E and AA. This is clear for primary resistance, but less for induced resistance. Switching from one exhausted pathway to another different one sounds wise, but deserves formal proof. Several mechanisms

might be involved, such as splice variants induction or androgen receptor-independent signaling pathways activation such as the phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT pathway, among others. None are well characterized to date.

For patients progressing after Doc both SLHT drugs are acceptable options, leading to a significant survival. This is not the case for Doc refractory patients (progression within 3 mo from the start of Doc) where Cab should be considered. These findings deserve further data to be fully convincing. When Cab is considered, although 25 mg/m<sup>2</sup> is the standard regimen, the lack of overall superiority and the increased toxicity compared with 20 mg/m<sup>2</sup> as seen in the PROSELICA trial [9] might lead to the reconsideration the optimal starting dose.

We are fortunate with this rapidly evolving situation. Survival is linked to the number of regimen used and is clearly improving. The androgen pathway remains a key driver but many others have to be considered. Also, postponing chemotherapy to the very end of the journey is clearly suboptimal. Finally, the early use of Doc in androgen-sensitive situations might change the overall landscape of mCRPC treatments.

This disease is complex and will be clarified through basic science. Treatment of such patients is optimized when all clinical partners are working together, including the basic scientists. No one is able to have all the needed knowledge.

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