MINI-REVIEW

Management of Non-metastatic castrate-resistant prostate cancer

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Abstract

When castration resistance is established, it is essential to rule out the presence of metastases or micrometastases by optimizing the use of imaging techniques. If non-metastatic castrate resistant prostate cancer diagnosis is confirmed the physician is in front of a difficult decision: to treat it or not and if not, how he can follow up his patient. In practice, patients awareness of their PSA levels and pressure to act upon any increase of PSA influence management irrespective of physical or radiographic findings. This highlights the need to have more accurate assessment of nmCRPC severity and the risk of progression. We review the literature about this ambiguous entity and we summarize all the available data for it’s management.

Introduction

Many patients with prostate cancer who are treated with curative intent (i.e. radical prostatectomy or radiation therapy) will experience a PSA recurrence. Although these men who have PSA recurrence are a heterogeneous group with a median overall survival of >23 years many urologists are reluctant to leave such a PSA recurrence untreated [1-3]. The main reason for this skepticism is that disease imaging is not always reliable for the detection of metastatic lesions and the most convenient management of this situation is to prescribe androgen deprivation therapy (ADT). A proportion of these patients will inevitably develop non-metastatic castrate resistant prostate cancer (nmCRPC). Even though there are significant challenges in the definition, assessment, risk stratification and management of patients with nmCRPC, the main goals remain the same: delay of initiation of chemotherapy and delay

Key words
prostate Cancer; castrate resistance; androgen deprivation therapy; non metastatic

Citation

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of progression to metastasis [5,6]. Moreover many patients classified as having nmCRPC may have testosterone above the level of castration [7] or may have metastases that standard imaging techniques failed to diagnose. Therefore, in order to optimize the management of nmCRPC, light must be shed to all aspects of this special condition.

What do we know for nmCRPC?

Literature lacks on data concerning the real prevalence of nmCRPC probably because most cases are declared based on PSA increase and therefore metastasis may be present but not immediately detected [8]. A recent systematic review of CRPC of more than 300 patients revealed that >84% of patients had metastasis at diagnosis and that nearly 1/3 of patients with nmCRPC will eventually develop bone metastasis in 2 years from diagnosis [9]. Data concerning the natural course of nmCRPC come from clinical studies with different regimens. The probably most useful insight come from a study comparing zoledronic acid vs placebo for nmCRPC which reports a metastasis free survival (MFS) of 30 months, 33% progression to mCRPC and 21% death rate in 2 years, all the above in the placebo arm [11].

Even though most recent clinical trials are struggling with high level of screening failures, conclusions can be drawn from their results. The most important from them is that PSA and PSADT values (>13ng/ml and <6 months respectively) can be useful in predicting possible outcomes and in reassuring patients [12,13]. However the precision of the above-mentioned tools in predicting define response and in guiding management decision is extremely low.

The value of imaging

The mainstay of bone metastases detection imaging remains conventional bone scintigraphy [14] even though it’s sensitivity in detecting bone metastases is lower than magnetic resonance imaging (MRI) [15]. The reasons for the abovementioned situation are cost, ease and the unclear impact of diagnosing metastasis a few months prior. Nevertheless, new imaging modalities emerge providing promising results. [11] C-choline PET/ CT or [68] Ga-labelled prostate specific membrane antigen(PSMA) can potentially detect metastases that conventional modalities fail to detect [16,17]. In a recent study there was a distinct correlation between PSA levels and detection rates of PSMA: 98,2% for PSA >2 ng/ml but only 57,9% for 0.2<PSA<0.5 ng/ml [18]. As for visceral metastases, computed tomography (CT) is the gold standard technique for their detection. Although visceral metastases in prostate cancer are relatively rare (5-10% of the patients), node involvement is much more common, and CT lacks significantly in detecting it. Whole body MRI with diffusion-weighted MRI may be useful for increasing detection rates of node metastases but more evidence is needed before this technique can be more widely adopted [19-20].

Management options and necessity

Current EAU guidelines strongly suggest not to treat nmCRPC outside clinical trials [21]. Since the goal of delaying the development of metastases and the initiation of chemotherapy, remains the same, many researchers conducted several studies suggesting different strategies with contradictory outcomes. One of these strategies is based on the fact that castrate resistant PCA maybe sensitive to some other hormonal manipulations [22] and it includes: alternative antiandrogen [23], antiandrogen removal [24], salvage antiandrogen therapy [25] and salvage LHRH therapy [26]. Unfortunately, despite the fact that these studies are reporting interesting results no secondary hormonal manipulation managed to alter the overall survival (OS) or the physical course of the disease and so neither EAU nor AUA guidelines suggest this strategy for nmCRPC [21,27].

The next field of study for nmCRPC was the potential role of the bone-targeted agents, that are used in combination with ADT, in altering the physical course of CRPC. A recent analysis has summarized most of them and concluded that these agents (clodronate, zoledronic acid, denosumab) didn’t improve neither OS nor MFS of the patients with nmCRPC, and even implicated with high rates of severe complications [28]. These data are not sufficiently robust to allow a recommendation for their use in nmCRPC and while hormonal agents
have been licensed for treatment of metastatic PCa, there is no evidence to support their use in a non-metastatic setting [29].

Since all known and widely adopted therapies, failed to prove their value for the nmCRPC, novel agents have emerged through clinical studies. ARN-509 and orteronel are two novel antiandrogens that were tested in the setting on CRPC with disappointing until now results [30-31]. Sipuleucel-T is a promising compound that was evaluated in an analysis of 2 RCTs: authors concluded that there is a trend toward better overall survival (4.3 months p=0.01) but no difference in time to disease progression between sipuleucel and placebo in nmCRPC patients. Similar results from a recent meta-analysis that included more than 700 patients with CRPC and report a prolonged overall survival with no benefit in MFS but for the metastatic CRPC [32]. Finally, Ogita et al studied the efficacy and safety of bevacizumab monotherapy in 16 patients with minimal or none impact in the physical course of the disease [33].

Based on the above-mentioned studies, the conclusion is that non-metastatic castration resistant prostate cancer must not be treated outside clinical trials. But the basic question is how to manage patients and how to schedule their follow up intervals. For these questions, Crawford et al along with the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group, are proposing an algorithm for M0 CRPC: 1st scan (CT and bone scintigraphy) when PSA ≥ 2 ng/ml and if this is negative then the next scan is scheduled when PSA reach 5 ng/ml. If the latter is also negative, then follow up visits of the patient are scheduled with 3 months intervals and a new scan will be performed every time PSA doubles [34].

Conflicts of interest
The author declared no conflict of interest.

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