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Anti-Tumour Treatment

Sequencing current therapies in the treatment of metastatic prostate cancer

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ABSTRACT

The standard treatment for metastatic prostate cancer is androgen deprivation therapy. However, progressive, metastatic disease usually develops, giving rise to metastatic castration-resistant prostate cancer (mCRPC). Great improvements have been made recently in the management of mCRPC, with current approved treatments including chemotherapy, androgen receptor-targeted agents, immunotherapies and radiopharmaceuticals. While the emergence of multiple effective therapies is encouraging, devising a treatment strategy can be difficult and it is becoming increasingly important, and challenging, to identify factors that influence the ideal timing of specific therapies. Considering where to place these agents in the treatment schedule of mCRPC, or whether these agents should be sequenced or combined to derive the optimal benefit for the patient, is not yet clear. Furthermore, cross-resistance may exist between these agents, which may ultimately influence treatment decisions and sequence choices. Preliminary data are emerging regarding the safety and activity for sequential treatment regimens, but there are currently no prospective studies. As prostate cancer is highly heterogeneous clinically, it is likely that no single treatment sequence will be optimal for all patients. However, at present, there are no validated biomarkers to guide individualized treatment for mCRPC. Here we review available data for the different mCRPC treatments, discussing potential sequencing of agents and possible cross-resistance or synergy among the recently approved and emerging therapies.

Introduction

For decades, the mainstay of first-line treatment for metastatic prostate cancer has been androgen deprivation therapy (ADT) [1]. ADT is initially effective for most patients, demonstrating the crucial role that androgens play in prostate cancer cell viability. However, progressive disease inevitably develops despite castrate levels of testosterone. Metastatic castration-resistant prostate cancer (mCRPC) is almost uniformly fatal, accounting for approximately 30,000 deaths in the US in 2014 [2]. Great improvements have been made over the past 10 years in the management of mCRPC, as several large trials using new therapeutic agents with diverse mechanisms of action have expanded the clinician's armamentarium [3–11]. While the emergence of several effective new therapies is encouraging, devising a treatment strategy can be perplexing, as optimal treatment varies based on the clinical scenario as well as the patient preferences.

The current array of approved treatments for mCRPC includes chemotherapy, androgen receptor (AR)-targeted agents, immunotherapies and radiopharmaceuticals [3–11]. In 2004, two landmark clinical trials comparing docetaxel chemotherapy to the previous standard of care demonstrated, for the first time, an overall survival (OS) benefit in patients with mCRPC [3,4]. More recently, a next-generation taxane, cabazitaxel, showed significant benefit in patients previously treated with docetaxel [5]. Despite progression in the castrate-state, a significant portion of the disease remains androgen-driven. Further inhibition of the AR axis using the lyase (CYP17) inhibitor abiraterone or the anti-AR agent enzalutamide can provide significant benefit for patients with mCRPC [6–9]. In addition, a prostate cancer vaccine, sipuleucel-T, and a radiopharmaceutical aimed at bone metastases, radium-223, have both demonstrated survival benefit in phase III clinical trials [10,11].

With multiple effective therapies now available, it is not yet clear how they should be sequenced or combined for optimal benefit. Nor is it yet fully understood whether cross-resistance among these agents exists and whether this should influence treatment decisions. Preliminary data are emerging regarding the safety and activity of sequential treatment regimens as well as data regarding

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markers of cross-resistance, but there are no prospective studies addressing these questions. Ongoing phase III clinical trials may provide answers. In this review, we address what is known regarding optimal sequencing of therapies for metastatic prostate cancer and describe possible cross-resistance and opportunities for combinations among the recently approved and emergent treatments.

Treating ADT-naive metastatic prostate cancer

Suppression of serum testosterone to castrate levels (via bilateral orchiectomy or treatment with a gonadotropin-releasing hormone [GnRH] agonist or antagonist) remains the backbone of therapy for metastatic prostate cancer (Table 1) [12,13]. Attempts have been made to successfully combine additional treatments with ADT to improve its effectiveness and the duration of response. Early-generation anti-androgens such as flutamide and bicalutamide are routinely used at the beginning of GnRH agonist treatment to avoid a testosterone flare phenomenon that can occur within the first two weeks of administration [14,15]. The effectiveness of prolonged combined androgen blockade using both a GnRH agonist and an anti-androgen has been more controversial. Combined androgen blockade appears to have certain advantages over ADT alone, such as improved response rate and pain control, though an association with longer disease-free survival and OS is less clear [16,17]. While one randomized trial with 1387 patients did not demonstrate improved survival outcomes for combined blockade [18], meta-analyses have suggested a modest 3% OS benefit at 5 years with anti-androgens, albeit with an increase in adverse events (AEs) such as diarrhea, fatigue and increased emotional lability [19–23]. Since toxicity and costs are higher and potential benefits uncertain, this approach is considered an option but not necessarily recommended [24]. Anti-androgens have a clearer role in the treatment of mCRPC, as discussed below.

The recent randomized controlled trial CHAARTED (ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) examined the addition of chemotherapy to standard ADT for metastatic ADT-naive disease [25]. This study demonstrated that combining docetaxel chemotherapy with standard ADT for metastatic prostate cancer was associated with improved outcomes compared with ADT alone. The trial included 790 men with prostate cancer metastases who had not received or had only recently initiated ADT. Men were randomized to receive ADT plus six cycles of docetaxel 75 mg/m^2 or ADT alone. Concurrent anti-androgen therapy was allowed. Median OS in the combination arm was 57.6 months versus 44.0 months in the ADT-only arm (hazard ratio [HR] 0.61; $p = 0.0003$). The docetaxel plus ADT regimen also proved beneficial when considering median time to clinical progression and median time to mCRPC. Notably, in a sub-group analysis, men with high-volume disease (defined by the presence of >4 bony lesions, including at least one lesion outside the vertebrae or pelvis, or the presence of visceral extra-nodal disease) had a median OS of 49.2 months in the combination arm versus 32.2 months in the ADT-only arm (HR 0.6; 95% confidence interval [CI] 0.45–0.81; $p = 0.0006$). This difference in outcome was not as profound in the sub-group with lower-volume disease (Table 1) [25].

Of note, a previous study evaluating ADT alone versus a combination of ADT plus docetaxel for patients with metastatic non-castrate prostate cancer (the GETUG15 trial) failed to show any OS benefit [26]. However, the two trials had important differences. In the CHAARTED trial, more patients were enrolled (790 versus 385) and the cases generally had higher-volume and higher-grade disease (high grade in 66% of patients in CHAARTED versus 22% in Gravis et al.) [25,26]. Although docetaxel was not associated with an OS advantage in GETUG15, it was associated with a delay in time to cancer progression. The use of early docetaxel is also being evaluated as one of several treatment arms in the STAMPEDE MRC trial (NCT00268476). The implementation of early docetaxel in routine practice is a patient-by-patient decision.

The mechanism underlying the effectiveness of combination therapy is not yet clear. It is hypothesized that cytotoxic chemotherapy attacks de novo ADT-resistant sub-populations of cancer cells at a time in the natural history of the disease when these cells remain vulnerable [27]. Additionally, the window of opportunity for treating patients with docetaxel will not be missed if it is given early in the course of disease, when performance status is better and chemotherapy is more easily tolerated [27]. Finally, pre-clinical studies have shown that a common pathway involving AR may be involved in the development of both castration resistance and taxane resistance. As a result, initial taxane

Table 1
Treatment choices for metastatic prostate cancer.

Metastatic castration-sensitive prostate cancer	Metastatic castration-resistant prostate cancer (mCRPC)			
	First-line treatment	Second-line treatment		Third- and fourth-line treatment
		Post-docetaxel	Post-AR-targeted agents	
• *ADT* • *ADT + docetaxel* strongly consider in the setting of high-volume disease	• *Abiraterone* • *Enzalutamide* • *Docetaxel* in the setting of symptomatic or visceral metastasis, or short time to CRPC • *Radium-223* in the setting of extensive, symptomatic bone disease and not fit for docetaxel • *Sipuleucel-T* in the setting of minimally symptomatic, low disease burden • *Clinical trial* Small-cell prostate cancer • Platinum-based chemotherapy Non-systemic treatment of metastatic prostate cancer • Radiation therapy at symptomatic sites	• *Abiraterone* • *Enzalutamide* • *Cabazitaxel* • *Radium-223* in the setting of extensive, symptomatic bone disease • *Sipuleucel-T* in the setting of slowly progressive disease • *Clinical trial*	• *Docetaxel* • *AR-targeting agent* abiraterone or enzalutamide • *Radium-223* in the setting of extensive, symptomatic bone disease • *Sipuleucel-T* in the setting of slowly progressive disease • *Clinical trial*	• *Chemotherapy* • *AR-targeting agent* abiraterone or enzalutamide • *Radium-223* • *Clinical trial* NB: (i) Clinical trials are recommended in all treatment settings. (ii) There are few prospective studies for third-line therapy; retrospective analyses suggest that cabazitaxel and enzalutamide have activity.

ADT = androgen deprivation therapy; AR = androgen therapy.