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TOPIC PAPER

Navigating systemic therapy for metastatic castration-naïve prostate cancer

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Abstract

Introduction The last decade has seen a remarkable shift in the treatment landscape of advanced prostate cancer, none more so than in the management of metastatic castration-naïve disease.

Methods This narrative review will examine existing and emerging evidence supporting systemic therapy use for metastatic castration-naïve prostate cancer (mCNPC) and provide guidance on the selection of these agents with respect to optimising patient outcomes.

Results The addition of either docetaxel (chemohormonal approach) or an AR pathway inhibitor (abiraterone, enzalutamide or apalutamide) is a reasonable standard of care option for men commencing long-term ADT for mCNPC. While the issue of disease volume as a predictive biomarker for docetaxel benefit has previously been debated, recent data support consideration of upfront docetaxel in all patients, regardless of metastatic burden. Decisions regarding systemic treatment for men with mCNPC should be based on comprehensive consideration of disease, patient and logistical factors. Multiple novel therapeutics for mCNPC are currently under active investigation.

Conclusion The introduction of potent systemic therapy earlier in the mCNPC disease course has resulted in dramatic improvements in clinical outcomes for patients. As the management of mCNPC continues to evolve, the future remains promising, with the expectation of ongoing improvements to patient outcomes and quality of life.

Keywords Metastatic prostate cancer · Castration-naïve · Hormone-sensitive · Androgen receptor pathway inhibitors · Docetaxel · Abiraterone · Enzalutamide · Apalutamide

Introduction

Despite advances in systemic treatment, metastatic prostate cancer carries a poor prognosis, with traditional 5-year survival estimates not exceeding 30% [1]. An appreciation of the critical role circulating androgens play in the progression of metastatic prostate cancer [2] led to the establishment of androgen deprivation therapy (ADT) as the standard of care for those with advanced disease. However, an awareness of aggressive tumour biology in a subset of patients has spurred significant efforts to explore the role of additional systemic therapy earlier in the disease course.

This review seeks to highlight key developments in the expansion of systemic therapies in metastatic castration-naïve prostate cancer (mCNPC). Furthermore, it will explore how the interplay of disease, patient and logistical factors influences treatment selection. Finally, we reflect on how progress in therapies for mCRPC are shaping future trials in the castration-naïve setting. It should be noted that

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"castration-naïve" is utilised in this review in preference to "castration-sensitive" or "hormone-sensitive" to describe prostate cancer not previously treated with ADT. Such terminology more accurately reflects the unknown sensitivity of prostate cancer to ADT in the initial phase of the condition, and better reflects the underlying mechanism of action of systemic therapy.

Evidence for systemic agents

Androgen deprivation

The mainstay of treatment for mCNPC remains depletion of systemic androgens, either by surgical or medical castration. ADT results in disease regression in ~ 90% of patients, but the median duration of response is only 12–24 months (mo). The optimal time to commence ADT in mCNPC remains controversial. Early ADT reduces symptoms due to disease progression and may extended overall survival (OS), but data are conflicting, impacted by clinical heterogeneity within many study cohorts [3]. Once commenced, the issue of intermittent versus continuous ADT remains a pertinent one, with the randomised, non-inferiority SWOG 9346 study unable to conclusively rule out the possibility that intermittent ADT may compromise outcomes in de-novo mCNPC, falling short of its primary endpoint [median OS (mOS) 5.1 years vs 5.8 years; hazard ration [HR] for intermittent therapy 1.10; 90% CI 0.99–1.23; non-inferiority margin of 20%]. In the absence of data supporting intermittent therapy, continuous ADT remains the standard of care in men with metastatic disease and forms the treatment backbone in landmark trials supporting the use of upfront systemic therapy in mCNPC.

ADT plus docetaxel

Three separate studies have sought to determine the role of upfront docetaxel with ADT in mCNPC (Table 1). The first, GETUG-AFU15, found no incremental benefit with the addition of up to nine cycles of docetaxel to ADT (mOS 58.9 mo vs 54.2 mo, HR 1.01; 95% CI 0.75–1.36), with evidence of greater toxicity with combination therapy [4]. In stark contrast, the ECOG3805 CHAARTED trial randomising 790 men with mCNPC to either ADT with docetaxel for six cycles or ADT monotherapy reported a dramatic 13.6 mo increase in OS (HR 0.61; 95% CI 0.47–0.80) [5]. Interestingly, unlike GETUG-AFU15, upfront stratification in CHAARTED included the extent of metastases, with high volume defined by at least four bone metastases (with at least one beyond the axial skeleton) or the presence of visceral metastases. This point of difference would prove to be critical, as subsequent analyses demonstrated improvements in outcomes were driven by the high-volume cohort (65% of the cohort), with little to no benefit in the low-volume subgroup [6]. Post-hoc examination of the GETUG-AFU15 cohort would reveal a similar observation (HR 0.78, 95% CI 0.56–1.09) [7], however, < 25% of patients fulfilled the CHAARTED high-volume criteria, raising the possibility that an underpowered analyses may have contributed to this statistically non-significant result.

STAMPEDE became the third landmark study reporting on chemohormonal therapy [8]. The addition of docetaxel to ADT significantly improved OS compared to ADT alone (HR 0.78, 95% CI 0.66–0.93), a relationship that persisted when the analysis was restricted to 1,817 men (61%) with metastatic disease (HR 0.76; 95% CI 0.62–0.92). In contrast to CHAARTED and GETUG-AFU15, which identified high disease burden as a therapeutic biomarker for benefit to docetaxel, recent updated long-term analysis of the STAMPEDE trial found no evidence of heterogeneity between the low and high metastatic burden subgroups across multiple outcome measures, including failure-free survival, progression-free survival (PFS) and OS [9]. Multiple meta-analyses of the aforementioned studies have since been published [10, 11], establishing docetaxel as the new standard of care for patients with mCNPC.

Table 1 Summary of results from phase III studies of docetaxel for mCNPC

DOCETAXEL			
	GETUG-AFU15 [7]	CHAARTED [5, 6]	STAMPEDE [9]
Overall	mOS: 62.1 vs 48.6 mo HR 0.88 (0.68–1.14)	mOS: 57.6 vs 47.2 mo HR 0.72 (0.59–0.89)	mOS: 59.1 vs 43.1 mo HR 0.76 (0.62–0.93)
High volume	mOS: 39.8 vs 35.1 mo HR 0.78 (0.56–1.09)	mOS: 51.2 vs 34.4 mo HR 0.63 (0.50–0.79)	mOS: 39.9 vs 35.2 mo 5yr OS: 34% vs 24% HR 0.81 (0.64–1.02)
Low volume	mOS: NR vs 83.4 mo HR 1.02 (0.67–1.55)	mOS: 63.5 vs NR mo HR 1.04 (0.70–1.55)	mOS: 93.2 vs 76.7 mo 5yr OS: 72% vs 57% HR 0.76 (0.54–1.07)

HR hazard ratio, *mo* months, *mOS* median overall survival, *OS* overall survival, *yr* year

ADT plus AR pathway inhibitors

Greater appreciation of the profound dependence of prostate cancer on androgen receptor signalling pathways has led to the development of therapeutic agents exploiting this vulnerability. Five studies exploring AR pathway inhibitors in mCNPC have now been reported (Table 2).

STAMPEDE (arm G) randomised 1,917 men to receive either ADT with abiraterone and prednisolone or ADT alone [12]. In patients with metastatic disease (M1; 52%), combination therapy resulted in a striking 39% improvement in OS (HR 0.61; 95% CI 0.49–0.75). In comparison, the LATITUDE trial examined a more homogenous population of de-novo mCNPC with high-risk features, defined by two or more of the following criteria: Gleason score ≥ 8, ≥ 3 bone lesions and presence of visceral metastases. The final analysis of this poor-prognostic group found the addition of abiraterone and prednisolone to ADT significantly prolonged OS by nearly 17 mo (HR 0.66; 95% CI 0.56–0.78) [13], though the magnitude of benefit may in part be explained by relatively low rates of subsequent treatment exposure at mCRPC development (57% in ADT monotherapy, 30% in combination). Meta-analysis of STAMPEDE (arm G) and LATITUDE demonstrated a cumulative 38% reduction in risk of death (HR 0.62; 95% CI 0.53–0.71) and a 14% absolute increase in OS at 3-year [14], and highlighted abiraterone and prednisolone as an alternative standard of care option in men with mCNPC commencing long-term ADT.

The impact of enzalutamide for mCNPC was recently explored in the ARCHES and ENZAMET trials [15, 16]. Both studies stratified by volume of disease and docetaxel use, a distinguishing factor to STAMPEDE (arm G) and LATITUDE, which excluded patients with prior docetaxel exposure. ARCHES randomised 1150 men to either ADT with enzalutamide or ADT alone, with the primary endpoint of radiographic PFS [15]. The addition of enzalutamide resulted in a 61% reduction in the risk of radiographic progression or death (HR 0.39; 95% CI 0.3–0.5), with benefit seen independent of disease volume and prior docetaxel exposure. Interestingly, the addition of enzalutamide did not appear to greatly increase rates of fatigue observed on the ARCHES study (all grade: 19.6% vs 15.3%). In contrast, ENZAMET enrolled 1125 men to either ADT with enzalutamide or ADT with a non-steroidal antiandrogen (NSAA) [16]. Distinct from ARCHES, the primary endpoint was OS, and patients planned for docetaxel received enzalutamide or NSAA concurrently (rather than sequentially) with chemotherapy. OS was significantly prolonged in the enzalutamide arm despite a more active control arm (HR 0.67, 95% CI 0.52–0.86), though at the expense of increased peripheral neuropathy (Grade 2: 9% vs 3%) and fatigue (Grade 2: 20% vs 14%) with concomitant docetaxel. Furthermore, the more serious albeit rarer side effect of seizures must also be acknowledged with enzalutamide (7 vs 0 patients). Intriguingly, while the benefit of enzalutamide appeared to be volume-agnostic (7% improvement in 3-year survival in high volume, 8% improvement in low volume), patients that received concurrent docetaxel did not appear to benefit from enzalutamide to the same extent (1% decline in 3-year survival with concurrent docetaxel and enzalutamide-treated, 13% improvement with enzalutamide alone), though the study was underpowered for this subgroup analysis.

Table 2 Summary of results from phase III studies of AR-targeted therapies for mCNPC

AR-targeted therapies					
	LATITUDE [13] (abiraterone)	STAMPEDE [12] (abiraterone)	ARCHES [38] (enzalutamide)	ENZAMET [16] (enzalutamide)	TITAN [17] (apalutamide)
Overall	HR 0.66 (0.56–0.78) mOS: 53.3 mo vs 36.5 mo	HR 0.62 (0.51–0.76) mOS: NR vs 34.7 mo	HR 0.39 (0.30–0.50) m-rPFS: NR vs 19.5 mo	HR 0.67 (0.52–0.86) mOS: NR vs NR 3-year OS: 80% vs. 72%	HR 0.39 (0.30–0.50) m-rPFS: NR vs NR 2-year OS: 82% vs 74%
High volume/risk	As per overall	HR 0.60 (0.45–0.78) by volume criteria HR 0.54 (0.41–0.74) by risk criteria	HR 0.44 (0.33–0.57) rPFS by volume criteria	HR 0.80 (0.59–1.07) by volume criteria	HR 0.68 (0.50–0.92) by volume criteria
Low volume/risk	Not applicable	HR 0.64 (0.42–0.97) by volume criteria HR 0.66 (0.44–0.98) by risk criteria	HR 0.24 (0.13–0.45) rPFS by volume criteria	HR 0.43 (0.26–0.72) by volume criteria	HR 0.67 (0.34–1.32) by volume criteria
Prior / planned docetaxel	Excluded	Excluded	18%	45%	11%
De-novo M1 disease	100%	49%	67%	58%	67%

HR hazard ratio, *mOS* median overall survival, *m-rPFS* median radiographic progression-free survival, *NR* not reached, *OS* overall survival, *rPFS* radiographic progression-free survival

Finally, the TTTAN study sought to compare apalutamide with placebo in mCNPC patients receiving continuous ADT [17]. Apalutamide reduced the risk of both co-primary endpoints: radiographic progression by 52% (HR 0.48, 95% CI 0.39–0.60) and the risk of death by 33% (2-year OS 82% vs 74%, HR 0.67; 95% CI 0.51–0.89). While rates of fatigue were numerically much lower than those observed in ENZAMET, apalutamide was accompanied by distinct toxicities of rash (all grade: 27% vs 9%) and hypothyroidism (all grade: 7% vs 1%). The study has subsequently been unblinded to allow crossover for control arm patients.

Multiple ongoing studies investigating the use of potent AR pathway inhibitors in mCNPC will report their findings in the coming years (Table 3), including combination abiraterone plus enzalutamide (STAMPEDE arm J), darolutamide (ARASENS) and orteronel (SWOG-1206). It is anticipated that many, if not all will meet their primary endpoint. In the absence of head-to-head data, cross-trial comparisons are inevitable, and small perceived differences in adverse event profile, together with local reimbursement constraints and patient preference are likely to play a significant role in the choice of agent to partner with ADT.

Treatment selection

While the addition of either docetaxel or an AR pathway inhibitor are both reasonable standard of care options for men commencing long-term ADT for mCNPC, direct comparative data is scarce with optimal management remaining largely undefined. STAMPEDE investigators attempted to address this clinical dilemma in a pre-specified but ultimately underpowered analysis of patients randomised over a discrete time period to either ADT plus docetaxel (arm C) or ADT plus abiraterone (arm G) [18]. This indirect comparative analysis significantly favoured treatment with abiraterone with respect to biochemical outcomes such as failure-free survival (HR 0.56, 95% CI 0.42–0.75) and disease progression (HR 0.69, 95% CI 0.50–0.95), but found no difference in OS (HR 1.13, 95% CI 0.77–1.66). Two subsequent network meta-analyses [19, 20] have also been published suggesting the high likelihood that abiraterone/prednisolone is superior to docetaxel in mCNPC, both in relation to PFS and OS, as well at the quality of life. Nevertheless, these studies cannot be regarded as substitutes for high-quality randomised controlled trials and, therefore, selection of optimal systemic therapy should be based on a comprehensive assessment of disease, patient and logistical factors (Table 4).

Disease factors

Disease volume and disease risk

The volumetric classification system of CHAARTED and the risk classification system of LATITUDE, provide a framework from which to guide decisions on treatment selection. In patients with high-volume/high-risk disease, studies support the use of either docetaxel or an AR pathway inhibitor (Table 2), with the final decision influenced by patient comorbidities and local access to therapy.

Table 3 Ongoing phase III studies of AR pathway inhibitors

Study name	Treatment arms	*N*	Primary endpoint	Study Identifier	Status
ARCHES	ADT +/- DOC ADT +/- DOC + ENZ	1150	rPFS	NCT02677896	Reported
ENZAMET	ADT +/- DOC + NSAA ADT +/- DOC + ENZ	1100	OS	NCT02446405	Reported
TITAN	ADT ADT + APA	1052	rPFS, OS	NCT02489318	Reported
PEACE-1	ADT +/- DOC ADT +/- DOC + AA/P ADT +/- DOC + prostate RT ADT +/- DOC + AA/P + prostate RT	1173	rPFS, OS	NCT01957436	Accrued, in follow up
STAMPEDE (arm J)	ADT +/- DOC ADT +/- DOC + AA/P + ENZ	1800	OS	NCT00268476	Accrued, in follow up
ARASENS	ADT + DOC ADT + DOC + DAR	1300	OS	NCT02799602	Accrued, in follow up
SWOG-1216	ADT + BIC ADT + ORT	1304	OS	NCT00268476	Accrued, in follow up

AA/P abiraterone/prednisolone, *ADT* androgen deprivation therapy, *APA* apalutamide, *BIC* bicalutamide, *DAR* darolutamide (ODM-201), *DOC* docetaxel, *ENZ* enzalutamide, *NSAA* non-steroidal antiandrogen, *ORT* orteronel (TAK-700), *OS* overall survival, *rPFS* radiographic progression free survival, *RT* radiotherapy

Table 4 Comparison of preferred treatment based on disease, patient and logistical factors

		Docetaxel preferred	Abiraterone preferred	Enzalutamide preferred	Apalutamide preferred	ADT monotherapy preferred
Disease factors	High-volume / high-risk disease	✓	✓	✓	✓	
	Low-volume / low-risk disease		✓	✓	✓	
Patient factors	Pre-existing cardiac dysfunction	✓		✓	✓	✓
	Pre-existing neuropathy		✓	✓	✓	
	Poorly controlled diabetes mellitus	✓		✓	✓	
	Poorly controlled hypertension	✓				
	Borderline performance status		✓	✓	✓	✓
	Contraindications to corticosteroids			✓	✓	
	Unfit for cytotoxic chemotherapy		✓	✓	✓	✓
	Prior seizures	✓	✓			
Logistical factors	Duration of therapy	✓				✓
	Cost	✓				✓
	Patient preference for oral treatment		✓	✓	✓	

ADT androgen deprivation therapy

In patients with low-volume/low-risk disease, systemic therapy selection is more complex. The STAMPEDE trial did not initially stratify based on disease volume or disease risk upfront, with docetaxel showing benefit in the all-comer population. However, a recent updated analysis of the study found no evidence that the benefit of docetaxel differed by metastatic burden, advocating that all mCNPC patients be considered for an upfront chemohormonal approach to systemic therapy [9]. In contrast, post-hoc analysis of CHAARTED [6] and GETUG-AFU15 [7] demonstrated no benefit to docetaxel in low-volume disease, though these studies may have been underpowered to draw definitive conclusions [21, 22]. Regardless, the decision to withhold docetaxel-based purely on disease volume alone (rather than additional patient factors such as comorbidities and performance status) should be cautioned in light of this more recent robust data. Furthermore, these studies underscore the need to distinguish the impact of definitions for disease risk versus disease volume.

The subject of differentiating between disease risk and volume was addressed in a post-hoc analysis of the M1 cohort of the STAMPEDE-abiraterone arm [23]. Though both classifications share similar features, discordance in risk/volume distribution was evident in 18% of patients (i.e. low-risk/high-volume, high-risk/low-volume). Despite this discordance, abiraterone demonstrated similar clinical benefit irrespective of risk or volume (Table 2), signifying such classifications as prognostic rather than predictive.

Crucially, distinct from STAMPEDE, the ARCHES, ENZAMET and TITAN trials stratified by disease volume. Collectively, these studies provide compelling evidence for benefit with enzalutamide and apalutamide independent of disease burden, arguing for AR pathway inhibitors to be the standard for low-risk/low-volume mCNPC. Without comparative data, the specific AR pathway inhibitor of choice should consider patient comorbidities and access issues (Table 4), as well as clinician familiarity with managing agent-specific adverse events (Table 5).

Though not the focus of this review, there is substantial overlap between low-volume disease and "oligometastatic" prostate cancer, typically defined by 1–5 sites of metastatic disease. Covered in greater detail in this edition of World Journal of Urology, metastases-directed therapy (MDT) techniques such as stereotactic ablative body radiotherapy (SBRT) [24-26] and salvage surgery [27-30] are now increasingly being investigated, especially in light of advances in novel molecular imaging offering unparalleled ability to detect distant disease. MDT holds obvious appeal, potentially delaying the need for systemic therapy, postponing the development of resistance to hormonal therapy and altering the natural course of a patient's disease [31]. Furthermore, evolving evidence now supports treatment of the primary disease in low-volume de-novo mCNPC [32, 33], not only as a avenue of preventing future local complications, but also to improve clinical outcomes [34].

De-novo disease versus recurrence after prior local therapy

De-novo metastatic disease represents a poorer prognostic group compared to patients that relapse after prior definitive therapy [22, 35]. Despite only representing 4% of all prostate cancers [36], de-novo metastatic disease disproportionately contributes to landmark trials, likely due to factors such

Table 5 Comparison of adverse events of interests amongst AR pathway inhibitors

	STAMPEDE [12]		ARCHES [38]		ENZAMET [16]		TITAN [17]	
	AA/P	PBO	ENZ	PBO	ENZ	NSAA	APA	PBO
Any AEs, n (%)	943 (99.5)	950 (99.0)	487 (85.1)	493 (85.9)	563 (100)	548 (98.2)	507 (96.8)	509 (96.6)
Any serious AEs, *n* (%)	443 (46.7)[a]	315 (32.8)[a]	139 (24.3)[a]	147 (25.6)[a]	235 (41.7)	189 (33.9)	104 (19.8)	107 (20.3)
AEs (all grades), *n* (%)								
Fatigue	648 (68.4)	551 (57.4)	138 (24.1)	112 (19.5)	465 (82.6)	363 (65.1)	103 (19.7)	88 (16.7)
Hypertension	299 (31.5)	131 (13.6)	49 (8.6)	36 (6.3)	118 (21.0)	70 (12.5)	93 (17.7)	82 (15.6)
Rash	135 (14.2)	85 (8.9)	15 (2.6)	9 (1.6)	41 (7.3)	27 (4.8)	142 (27.1)	45 (8.5)
Falls	0 (0)[b]	0 (0)[c]	21 (3.7)	15 (2.6)	54 (9.6)	20 (3.6)	39 (7.4)	37 (7.0)
Fractures	0 (0)[b]	0 (0)[c]	37 (6.5)	24 (4.2)	22 (3.9)	10 (1.8)	33 (6.3)	24 (4.6)
Cognitive / memory impairment	61 (6.4)	36 (3.8)	26 (4.5)	12 (2.1)	75 (13.3)	23 (4.1)	NR	NR
Seizures	4 (0.4)	3 (0.3)	2 (0.3)	2 (0.3)	7 (1.2)	0 (0)	2 (0.4)	1 (0.2)

AA/P abiraterone/prednisolone, *AE* adverse event, *APA* apalutamide, *ENZ* enzalutamide, *NR* not reported, *NSAA* non-steroidal antiandrogen, *PBO* placebo

[a]Patients with Grade 3–5 adverse events

[b]Missing data from 489 (52%) patients

[c]Missing data from 629 (66%) patients

as reduced prostate-specific antigen (PSA) screening and greater use of ADT at biochemical relapse.

Patients with M1 disease and prior local therapy were underrepresented in both docetaxel trials (24-32% in GETUG-AFU15 [4], 27% in CHAARTED [5], 4% in STAMPEDE arm C [8]) and AR pathway inhibitor trials (3% in STAMPEDE arm G [12], 0% in LATITUDE [37], 42% in ENZAMET [16], 33% in ARCHES [38] and 16% in TITAN [17]). Consequently, any conclusions regarding the efficacy of systemic therapy based on de-novo versus relapsed disease should be viewed with caution. In docetaxel trials, the greatest benefit was seen in patients with de-novo/high-volume and relapsed/high-volume disease, with modest to no benefit seen in de-novo/low-volume and relapsed/low-volume subgroups [6, 22]. Comparatively, the use of AR pathway inhibitors was most compelling in patients with de-novo disease, regardless of volume status [13, 16, 17, 23, 38], though patients with relapsed disease also appeared to benefit from treatment. Therefore, treatment decisions based exclusively on whether patients exhibit de-novo versus relapsed disease are not recommended.

Patients that relapse after prior definitive therapy with low volume/risk disease represent a favourable prognostic subgroup that may benefit from novel treatment strategies, including radiation to the prostate primary and MDT (both discussed in this issue of World Journal of Urology). Such approaches may be particularly efficacious in those with prolonged disease-free interval after definitive therapy, with accompanying favourable PSA kinetics. Whether local ablative therapies need to be combined with short periods of systemic therapy (e.g. ADT, AR pathway inhibitors) is still unknown.

Response to initial ADT

Depth of biochemical response to initial ADT may influence the decision to commence additional systemic treatment. Multiple studies have now validated 7-month PSA as a prognostic biomarker in mCNPC treated with ADT [39, 40], with the ability to achieve undetectable PSA levels (< 0.2ng/ml) strongly correlating with excellent prognosis, and conversely, poor prognosis in patients with a PSA nadir > 4ng/ml. Most mCNPC studies of docetaxel or AR pathway inhibitors allowed for up to 3–6 mo of ADT to be administered before randomisation. Initial biochemical response to ADT could feasibly by monitored, with systemic therapy reserved only in the setting of suboptimal PSA reduction. This approach may possess significant clinical utility in patients with borderline performance status, or in countries where access to AR pathway inhibitors is limited due to lack of financial reimbursement.

Patient factors

In the absence of prospective randomised studies comparing active agents, treatment selection will primarily depend on a patient's comorbidities and predicted tolerability to systemic therapy.

Docetaxel

An assessment of general fitness for cytotoxic chemotherapy is required before embarking on docetaxel treatment. In the CHAARTED and STAMPEDE studies, 14–29% of patients were unable to complete their six cycles of

docetaxel, highlight the difficulty of the regimen. In general, patients with performance status ≥ 2 (underrepresented in landmark trials), moderate peripheral neuropathy and those deemed unlikely to tolerate an episode of neutropenic sepsis should avoid docetaxel treatment. Furthermore, biological age rather than chronological age should be used to base decisions on chemotherapy administration.

Abiraterone

Cardiovascular toxicity is arguably the most clinically significant adverse event associated with abiraterone. Meta-analysis demonstrates a three-fold increase in grade 3–4 acute cardiac toxicity and a two-fold increase in grade 3-4 vascular toxicity, with the latter driven predominantly (> 90%) by the development of hypertension. Abiraterone should be avoided in patients with uncontrolled hypertension, congestive heart failure (ejection fraction < 50%), active ischaemic heart disease and recurrent symptomatic arrhythmias. Furthermore, given the 12-15% incidence of any grade hepatotoxicity in STAMPEDE and LATITUDE [12, 37], abiraterone may not be suitable in patients with moderate to severe hepatic impairment. Given the small dose of concurrent prednisolone (5mg) used in the pivotal studies, abiraterone use should not be excluded based on the presence of brittle diabetes alone.

Enzalutamide

Enzalutamide is most well-recognised for its central nervous system side effects, notably fatigue, cognitive/memory impairment and seizures. In patients with known cognition issues, the decision to commence enzalutamide will depend on the level of baseline impairment. The mechanism by which enzalutamide causes seizures is related to inhibition of γ-aminobutyric acid (GABA)-gated chloride channels. Prior history of seizures, regardless of subtype is an absolute contraindication to enzalutamide use. Furthermore, patients with a condition that predisposes to seizures (e.g. cerebrovascular accident, traumatic brain injury, dural-based metastases) or on medications that lower seizure threshold (e.g. antidepressants, tramadol) should be treated with an alternate systemic therapy option. Caution should be exercised when commencing enzalutamide in patients with poor mobility or balance issues, as falls were observed more commonly in the experimental arms of ARCHES [15] and ENZAMET [16]. Finally, concurrent use of enzalutamide and docetaxel should be avoided in patients with pre-existing neuropathy, given the significantly higher rates of peripheral neuropathy seen on the ENZAMET study [16].

Apalutamide

With a chemical structure similar to enzalutamide, apalutamide shares the same precautions and contraindications as described above. In the SPARTAN study [41] of non-metastatic castration-resistant prostate cancer patients, a significantly greater incidence of falls and fractures was observed in the apalutamide arm. In the corresponding mCNPC TITAN study [17], the difference in these adverse events between the apalutamide and placebo arm were less striking, though still maintained a numerical higher rate in the active therapy group. Apalutamide may not be the optimal agent for patients with a history of recurrent falls or osteoporosis. Close monitoring of thyroid function tests is warranted, particularly in patients on pre-existing thyroxine replacement therapy.

Logistical factors

Patient preference

Patient preference should play a significant role in decisions regarding treatment selections. Where flexibility and tolerability are desired, oral AR pathway inhibitor therapy may be preferred over intravenous docetaxel. Conversely, patients prioritising finite duration on therapy may opt for six cycles of docetaxel (18-week course) over the extended time of treatment observed with abiraterone (33 and 24 months in STAMPEDE and LATITUDE respectively). Similar time on treatment is expected for enzalutamide and apalutamide with more prolonged follow-up of ARCHES, ENZAMET and TITAN. Ongoing research on patient-reported outcomes and quality of life measures in advanced prostate cancer will enable care providers to place greater emphasis on understanding motivations that drive patient treatment preferences.

Local availability and cost of systemic therapy

Access to new systemic therapies for advanced prostate cancer remains a major issue across the world, particularly in low and middle-income countries [42]. In situations where drug may be accessible, factors surrounding lack of financial reimbursement are likely to influence prescribing practices [43], particularly with docetaxel holding a significant cost advantage over AR pathway inhibitors in the absence of generic products [44].

Emerging impact of novel imaging

Traditional prostate cancer radiographic staging involves CT imaging and bone scintigraphy, despite poor sensitivity and specificity for both bone and lymph node disease alike [45,

46]. Functional imaging using new PET radiotracers such as 11C-choline, 18F-fluciclovine and more recently 68Ga-PSMA have led to earlier detection of recurrent disease and granting opportunities to institute effective salvage therapies [47], with the latter discussed in this edition of World Journal of Urology.

The full implications of PSMA PET/CT on clinical care are only beginning to be realised [48]. With significant stage migration expected, the risk of extrapolation of pre-existing data guiding management strategies (historically based on conventional imaging) is high. A collaborative approach to researching optimal incorporation of novel imaging into clinical practice is a major priority. More sensitive imaging techniques will enable identification of individuals most likely to benefit from MDT and timely systemic therapy for those who will not.

Novel therapeutic combinations

With AR pathway inhibitors likely to continue to dominate the mCNPC treatment landscape, one may anticipate that new strategies will incorporate active mCRPC agents into the earlier disease space.

Promising activity has been seen with poly(ADP-ribose) polymerase (PARP) inhibitors in mCRPC patients harbouring DNA repair mutations [49]. Interestingly, the benefit may not be restricted to this patient subgroup [50]. While studies of these agents in the neoadjuvant and biochemical relapse setting are currently in progress, no studies exist in mCNPC. This may change if efficacy in the mCRPC can be confirmed in late-phase studies.

Theranostics, the concept of integrating diagnostic imaging into the design of clinical therapeutics is also being explored in advanced prostate cancer. A recent single-arm phase II trial of ^{177}Lu-PSMA radionuclide treatment in heavily pre-treated mCRPC showed encouraging activity with minimal toxicity [51]. Ongoing studies investigating ^{177}Lu-PSMA compared with cabazitaxel (NCT03392428) and best supportive care (NCT03511664) are now underway. If positive, ^{177}Lu-PSMA may find a role in mCNPC in combination with docetaxel and/or AR pathway inhibitors.

Preliminary reports of activity to single-agent immune checkpoint inhibitors in prostate cancer have been modest, with overall response rates to single-agent PD-1 or CTLA-4 blockade of < 10% in molecular unselected individuals with mCRPC [52, 53]. Combined dual checkpoint inhibition may improve responses but at the expense of increased toxicity [54]. Future studies will likely investigate the optimal timing and dosing of combination immunotherapeutic strategies in mCNPC, employing unique approaches to improving tumour immunogenicity in this condition (e.g. vaccines, adoptive cell therapies).

Conclusion

The introduction of potent systemic therapy earlier in the mCNPC disease course has resulted in dramatic improvements in clinical outcomes for patients. The selection of docetaxel or AR pathway inhibitors requires consideration of both diseases, patient and logistical factors. The emergence of molecular imaging techniques such as PSMA PET/CT continues to redefine clinical disease states, heralding a new wave of therapeutic options, including treatment to the primary tumour, MDT and radionuclide theranostics. Going forward, as data emerges supporting innovative combinational strategies in mCRPC, it will be critical to adopt a cautious and methodical approach to translating benefits into the mCNPC space. In a world of finite resources and ongoing issues with drug access, the search for predictive biomarkers to new and existing treatments remains relevant. Regardless, the future is a promising one, for it is expected that the management of mCNPC will continue to evolve greatly over time.

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Compliance with ethical standards

Conflict of interest Edmond M Kwan has received honorarium from Janssen; research funding from Astellas Pharma and AstraZeneca; travel / accommodation from Astellas Pharma, Pfizer and Ipsen. Arun A Azad is a consultant for Astellas, Janssen and Novartis; is on the speakers bureau for Astellas, Janssen, Novartis and Amgen; has received honorarium from Astellas Pharma, Janssen, Novartis, Tolmar, Amgen, Pfizer and Telix; on the member of the scientific advisory board for Astellas, Novartis, Sanofi, AstraZeneca, Tolmar, Pfizer and Telix; research funding from Astellas Pharma and Merck Serono. All authors declare no conflicts of interest.

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