



Current treatment options for newly diagnosed metastatic hormone-sensitive prostate cancer – a narrative review

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Abstract: Prostate cancer continues to be one of the most commonly diagnosed cancers in men globally and a leading cause of male cancer deaths. The landscape of metastatic hormone-sensitive prostate cancer has significantly changed over the past decade. For many years, androgen deprivation therapy alone through surgical or chemical castration was the mainstay of treatment yielding limited 5-year survival rates. New treatment approaches using Docetaxel chemotherapy or androgen receptor pathway inhibitors to intensify upfront systemic therapy have resulted in significantly improved survival rates compared to androgen deprivation therapy alone. Clinicians are now equipped with an arsenal of drugs capable of prolonging life for metastatic hormone-sensitive prostate cancer patients. Furthermore, new treatment modalities are being tested in clinical trials making treatment of metastatic hormone-sensitive prostate cancer an extremely dynamic space. In this narrative review, we provide an overview of the key systemic treatments for metastatic hormone-sensitive prostate cancer, namely androgen deprivation therapy, novel androgen receptor pathway inhibitors and Docetaxel. We summarise a series of landmark trials that have led to the integration of novel androgen receptor pathway inhibitors and docetaxel into the treatment paradigm for metastatic hormone-sensitive prostate cancer. Lastly, we discuss nursing, financial and side-effect considerations pertaining to the use of these drugs. This article aims to give its readers an understanding of the evidence and clinical aspects of novel therapies in metastatic hormone-sensitive prostate cancer as they become increasingly available for use around the world.

Keywords: Prostate cancer; metastatic; hormone-sensitive; management

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Introduction

Prostate cancer incidence has risen all around the world, including in the Asia-Pacific region where it now accounts for more than 120,000 deaths per annum (1). However, incidence varies with low rates observed in South and East Asia, contrasted with higher rates observed in South East Asia, and among the highest rates in the world reported in Australia (2). Despite being extremely treatable in its early stages, prostate cancer still remains a leading cause of cancer-related death worldwide (3), and in Australia, is the second leading cause of male cancer-related deaths (4). Of these men, approximately one third presented with newly diagnosed or de novo metastatic prostate cancer and two thirds relapsed after prior local therapy (5). Advanced stage prostate cancer continues to have a poor prognosis which is reflected by a five year survival rate of 31–36% (6,7).

Androgen deprivation therapy (ADT) has been at the forefront of treatment for metastatic prostate cancer since the Nobel prize winning works of Huggins and Hodges. Unfortunately, although effective at first, all patients inevitably develop a rising PSA or new metastases despite castrate levels of testosterone. This marks the transition to a lethal form of prostate cancer known as castration-resistant prostate cancer (CRPC). The discovery of new androgen receptor pathway inhibitors (ARPIs) and the utility of taxane based chemotherapy in the CRPC setting has resulted in significant gains in overall survival (OS). These agents have more recently been tested for metastatic hormone-sensitive prostate cancer (mHSPC), with all of Docetaxel, Abiraterone, Enzalutamide and Apalutamide yielding significant improvements in OS. This has led to changes in treatment guidelines, approvals and subsidies across the globe.

Given the number of options at our disposal, it is paramount that clinicians have an understanding of new agents, their side effect profile and when to prescribe them. Here we review the current treatment options for mHSPC, discuss decision-making considerations and outline future clinical trials that may alter management of this condition.

We identified the treatment options available for use in mHSPC treatment as well as important clinical aspects including nursing, financial and other decision-making considerations. A search was then performed in PubMed and Google Scholar for the most recent and relevant articles pertaining to the topics identified. An emphasis was placed on phase 3 clinical trials for inclusion into our article. Clinicaltrials.gov was utilised to identify ongoing and future

trials for mHSPC. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tau-20-1118>).

Traditional androgen deprivation therapy agents (Table 1)

LHRH agonist

Luteinizing hormone-releasing hormone (LHRH, also known as gonadotropin releasing hormones) is released by the hypothalamus and stimulates the anterior pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (8) ultimately producing testosterone. It was first discovered and then isolated by two Nobel prize winners—Schally and Guillemin—in the late 1960s/early 1970s. Over the next 20 years LHRH was recognised as being a clinically relevant target for hormone-sensitive cancers such as breast cancer and prostate cancer. Pioneers in the field made significant advancements that culminated in the approval of the first LHRH agonist (triptorelin) for use in prostate cancer in 1986 (9).

LHRH agonists disrupt the normally pulsatile release of LHRH from the hypothalamus and over time result in a downregulation of LH with testosterone reaching castration levels at around 3–4 weeks (10). Unfortunately, there is an initial flare or surge of testosterone causing a transient increase in tumour volume. This can have a clinical effect causing urinary obstruction, bone pain and even spinal cord compression (11). The effects of testosterone flare can be mitigated by the short-term use of a first-generation anti-androgen such as bicalutamide.

LHRH antagonists

The development of LHRH antagonists combatted the initial “flare” or “surge” effect of testosterone from LHRH agonists. LHRH antagonists bind directly to LHRH receptors in the pituitary, thus provoking an immediate blockade of LH and a fast decrease in testosterone levels without the flare phenomenon (11). Abarelix was the first approved LHRH antagonist, however studies found significant clinical adverse effects such as severe hypersensitivity reactions and escape from castration that subsequently led to its cessation of use (7,12). Since then, a new and improved third generation LHRH antagonist, degarelix, has become the mainstay of LHRH antagonist treatment. Klotz *et al.* compared the efficacy and tolerability

Table 1 Medications for mHSPC

Class of drug	Common	Mechanism of action	Adverse effects
LHRH agonists	Leuprolide, Goserelin	Disrupt normally pulsatile release of LHRH from hypothalamus producing downregulation of testosterone over time	Initial flare of testosterone and transient increase in tumour volume, decrease bone and muscle mass, decrease insulin sensitivity, increased cardiovascular events, hot flushes, gynaecomastia, decreased sexual function, mental health issues
LHRH antagonists	Degarelix	Bind directly to LHRH receptors in pituitary provoking fast decline in testosterone	Decrease bone and muscle mass, decrease insulin sensitivity, increased cardiovascular events, hot flushes, gynaecomastia, decreased sexual function, mental health issues
Steroidal ARPIs	Abiraterone	Inhibits P450 c17 (CYP17)—a critical enzyme in androgen synthesis pathway	Cardiac and hepatic toxicity, hypertension
Non-steroidal ARPIs	Enzalutamide, Apalutamide, Darolutamide	Competitive inhibitor of androgen receptor, inhibits nuclear translocation of androgen receptor, inhibits co-activator transport, inhibits DNA binding	Neutropenia, anaemia, fatigue, cognitive issues, cardiovascular events, seizures
Taxane-based chemotherapy	Docetaxel, Cabazitaxel	Binds to protein (tubulin) found in microtubules of cells	Neutropenia, alopecia, nail changes, sensory neuropathy, peripheral oedema, diarrhoea

LHRH, luteinizing hormone releasing hormone; ARPI, androgen receptor pathway inhibitors; mHSPC, metastatic hormone-sensitive prostate cancer.

of degarelix to leuprolide in 610 men with hormone-sensitive prostate cancer. The authors found that >95% patients taking degarelix were able to reach castration levels (testosterone <0.5 ng/mL) by day 3. Degarelix also displayed the same ability to maintain these levels over 1 year compared to LHRH agonists (13). Most recently, an oral third generation LHRH antagonist relugolix was proven to be superior to leuprolide in achieving rapid and sustained testosterone suppression (14). Over 96% of men who received relugolix maintained castration through to 48 weeks as compared to 88% in the leuprolide group. Moreover, 56% of men reached castration levels at day 4 with relugolix (14). Of particular note, relugolix was also associated with a 54% relative risk reduction in major adverse cardiovascular events as compared to leuprolide.

Adverse effects

In spite of their proven benefit for prostate cancer patients, traditional ADT agents can have considerable adverse effects pertaining to their hormonal manipulation. ADT decreases serum testosterone levels by >95% and by doing so gives rise to a number of physiological alterations. A change in bone and muscle homeostasis, lipid profile, hypertension and insulin sensitivity can lead to fractures,

diabetes and cardiovascular events (14,15). Other side effects include hot flushes, gynaecomastia, sexual dysfunction and mental health issues (16).

Androgen receptor pathway inhibitors (ARPI)

The initial management for metastatic prostate cancer is surgical or medical castration via ADT. Nearly all patients initially respond but resistance is inevitable, indicated by a rising PSA level, new lesions, and/or progressive symptoms. This lethal phenotype is referred to as CRPC but remains driven by persistent androgen receptor (AR) signalling (17). Numerous mechanisms have been implicated in persistent AR signalling in CRPC including AR gene amplification, AR gene mutations, AR splice variants, extra-gonadal androgen synthesis, increased expression of AR co-regulators and non-AR signalling pathways that cross-talk with the AR. A greater understanding of the role of the AR in development of CRPC underpinned efforts to more effectively target androgen signalling using ARPIs.

ARPIs have been investigated and refined since the 1960s. Steroidal ARPIs have a similar chemical structure to testosterone and progesterone and therefore can have unintended hormonal side effects not relating to prostate cancer treatment. Non-steroidal ARPIs have a

distinct chemical structure and therefore do not exhibit progesterone related side effects and are more tailored as a pure AR blocker.

Non-steroidal ARPIs have progressed through decades of research. They exert their effect at a cellular level by competitively binding to the androgen receptor thereby inhibiting testosterone and dihydrotestosterone from activating their biological reactions. First generation non-steroidal ARPIs such as bicalutamide, although effective at first, had flaws. They have a low affinity for the AR (18) but perhaps most concerning was their agonist effect that were in some cases when castration resistance ensued (19,20).

Second generation non-steroidal ARPI—such as Enzalutamide, Apalutamide and Darolutamide—have a greater affinity for the AR than first-generation ARPIs and have no known or minimal agonistic effects. Along with being a competitive inhibitor of the AR, these agents combat increased AR gene expression by inhibiting nuclear translocation of the AR, DNA binding, and coactivator recruitment (21). Enzalutamide showed superior OS in both chemotherapy-treated and chemotherapy-naïve mCRPC patients (21,22). Apalutamide is a non-steroidal ARPI with the same mechanism of action as Enzalutamide but the added benefit of having less penetration of the blood brain barrier. In addition to this, early evidence suggests that apalutamide may not increase the frequency of AR anomalies that contribute to castrate resistance (23). Darolutamide is another second generation non steroidal ARPI that is a potent AR inhibitor but is structurally different from Enzalutamide and Apalutamide. This accounts for its negligible blood brain barrier penetration and theoretically less CYP drug interactions in pre-clinical models (24).

Abiraterone is a second generation steroidal ARPI that inhibits a critical enzyme in androgen synthesis named P450 c17 (CYP17). By doing so, Abiraterone is able to decrease testosterone produced by the adrenal gland and also intracellularly in prostate cancer cells. It has also shown antagonistic and downregulatory effects of AR (25). Like Enzalutamide, Abiraterone has demonstrated significant improvements in OS for both chemotherapy-treated and chemotherapy-naïve mCRPC patients (26,27).

Taxane based chemotherapy

Taxane based chemotherapy has been the mainstay of chemotherapy for metastatic prostate cancer since 2004 when Docetaxel was shown to significantly improve OS

in mCRPC over mitoxantrone in the TAX-327 trial (28). Taxanes act by binding to tubulin, a protein found in microtubules of cells. By doing so, taxanes stabilise the microtubules not allowing them to disassemble and carry out their normal functions including vesicle transport, transcription factor trafficking, cell signalling and chromosome separation during cell division (mitosis) (29).

Combination trials (Table 2)

Given the proven activity of Docetaxel and ARPIs in mCRPC, multiple clinical trials were then initiated to look at the activity of these agents when used upfront with ADT in mHSPC. Although key differences exist between these trials in regards to treatment combinations and inclusion of specific patient sub-groups, overall these studies have shown a major benefit with intensification of upfront systemic treatment of mHSPC. Of note, the definition of high volume/high risk metastatic prostate cancer has not yet been universally defined. The two main criteria derived from the CHAARTED trial and LATITUDE trial is shown in Table 3.

Docetaxel plus ADT

Three large randomised trials have studied the efficacy of Docetaxel compared to standard therapy in mHSPC patients.

The GETUG-AFU 15 trial was a randomised phase 3 trial run in 29 centres throughout France and Belgium. 385 men with mHPSC were recruited and were randomised to receive ADT plus a non-steroidal ARPI or Docetaxel (75 mg/m² intravenously on the first day of each 21-day cycle; up to nine cycles) without prednisone. In this study, with a median follow up of 50 months, there was no statistically significant difference in OS between the two treatment arms. However, biochemical and radiographic PFS was significantly prolonged in the Docetaxel arm (30). An updated report of the analysis revealed that at median follow up of 83.9 months, median OS was 62.1 months and 48.6 months in the Docetaxel plus ADT and ADT arms respectively (31). These conflicting results may have been due to the inclusion of a relatively large percentage of low volume metastatic disease (52% low volume disease defined using CHAARTED criteria). In the Docetaxel plus ADT group, 39 of 189 (21%) patients discontinued treatment due to toxicity effects. Neutropenia (32% of patients in this arm), febrile neutropenia (7%), fatigue (7%), erectile

Table 2 Combination drug trials

Combination drug	Trial name	Number of patients	Dose	Control arm	Prior local therapy (%)	High volume/risk (%)	Prior concurrent Docetaxel (%)	Median follow up (months)	OS	Discontinued due to adverse effect (%)	Notes
Docetaxel	GETUG-AFU 15	385	75 mg/m ² IV 3 weekly up to 9 cycles	ADT plus non-steroidal ARPI	NR	48	Excluded	83.9	Median OS 13.5 months longer in Docetaxel arm	21	
	CHAARTED	790	75 mg/m ² IV 3 weekly for 6 weeks	ADT	28	65	Excluded	53.7	Median OS 10.4 months longer in Docetaxel arm	14	
	STAMPEDE	1,776	75 mg/m ² IV 3 weekly for 6 weeks	ADT	6	60	Excluded	43	Median OS 15 months longer in Docetaxel arm	13	OS for metastatic disease only
Abiraterone	LATITUDE	1,199	1,000 mg daily with 5mg daily prednisone	ADT plus placebo	0	100	Excluded	51.8	Median OS 16.8 months longer in Abiraterone arm	16	High risk patients only
	STAMPEDE	1,917	1,000 mg daily with 5mg daily prednisone	ADT	5	55	Excluded	40	Hazard ratio for death 0.61 (P<0.001)	NR	OS of metastatic disease only
Enzalutamide	ENZAMET	1,125	160 mg daily	ADT plus standard of care non-steroidal ARPI	42	52	45	34	Hazard ratio for death 0.67 (P=0.002)	6	
	ARCHES	1,150	160 mg daily	ADT plus placebo	27	63	18	14.4	OS statistics not yet mature. Risk of radiographic disease progression reduced by 61% in Enzalutamide arm	7	
Apalutamide	TITAN	1,052	240 mg daily	ADT plus placebo	19	63	11	22.7	Hazard ratio for death 0.67 (P=0.005)	8	

ADT, androgen deprivation therapy (surgical castration, LHRH agonist or LHRH antagonist); ARPI, androgen receptor pathway inhibitor; OS, overall survival; NR, not reached/reported.

Table 3 High volume/risk criteria for metastatic prostate cancer

CHAARTED high volume criteria	LATITUDE high risk criteria
>4 bone metastases (at least one outside the spine or pelvis) AND/OR Visceral metastases	Two or more of the following criteria: <ul style="list-style-type: none"> • >3 bone metastases • Gleason score >8 • Visceral metastases (not including lymph node metastases)

dysfunction (8%), and decreased libido (6%) were the most common grade 3–4 adverse effects recorded (32).

The CHAARTED trial enrolled 790 men with mHSPC to receive either ADT or ADT plus Docetaxel (75 mg/m² intravenously every 3 weeks for six weeks) plus dexamethasone. In both arms, median age of patients were around 63–64 years and approximately 70% of patients had ECOG performance status of 0. Around 65% of patients had high volume disease and in both arms, 72.8% of patients had received no previous local therapy and therefore were considered to have de novo metastatic disease. At median follow up of 28.9 months, median OS was found to be 13.6 months longer in the Docetaxel arm (56.7 *vs.* 44 months). The median time to clinical progression was found to be 33 months in the Docetaxel arm compared to 19.8 months in the ADT only arm (32). More mature results at median follow up of 53.7 months showed median OS was 10.4 months longer in the Docetaxel arm for all patients. Survival benefit was more pronounced in high volume disease patients (16.8 months longer OS in Docetaxel arm), however in contrast survival benefit in low volume disease was not demonstrated (33). It should be noted that the statistical design of CHAARTED was not powered to show a survival benefit in patients with low volume disease. In this trial, 86% of patients completed six cycles of Docetaxel therapy. Neutropenia (12%), febrile neutropenia (6%), fatigue (4%), infection with neutropenia (2%) and allergic reaction (2%) were the most common grade 3–4 adverse effects reported in the Docetaxel arm.

The STAMPEDE trial is the largest and most recent trial to analyse the effects of Docetaxel. In a multi-arm, multi-stage design, the STAMPEDE group recruited 2,962 men with hormone-sensitive prostate cancer to be randomised to receive ADT, ADT plus Docetaxel (75 mg/m² intravenously every 3 weeks for six weeks) plus prednisolone, ADT plus zoledronic acid or ADT plus Docetaxel plus zoledronic acid. Median age of men in all arms were around 65 years and almost all men (94%) had newly diagnosed prostate cancer.

61% of men had metastatic disease and the remaining 39% had locally advanced disease. Zoledronic acid was not shown to have any survival benefit. At median follow up of 43 months, the Docetaxel arm and Docetaxel plus zoledronic acid arm showed 10 and 5 months respectively longer median OS compared to ADT for all patients. In a subgroup analysis of patients with metastatic disease, the Docetaxel arm showed median OS was 15 months longer compared to ADT only (34). The Docetaxel and Docetaxel plus zoledronic acid arms both recorded 13% of patients discontinue treatment due to toxicity. Adverse effects were also similar in both arms with febrile neutropenia (15%), endocrine disorders (10–12%), neutropenia (10%), general disorders (7–11%), and gastro-intestinal disorders (7–8%) being the most commonly reported grade 3–4 adverse effects (34).

Abiraterone plus ADT

Abiraterone was the first of the novel ARPIs to be trialled and proven in the mHSPC setting.

The LATITUDE trial was an international placebo controlled, randomised phase 3 trial analysing Abiraterone. This group assigned 1,199 men with high risk mHSPC (at least two of the following prognostic factors: Gleason score 8 or higher, 3 or more bone metastases, or measurable visceral metastases) to receive ADT plus Abiraterone 1,000 mg daily plus prednisone 5 mg daily versus placebo. At a median follow up of 30.4 months, the 3-year OS rate was 66% and 49% in the Abiraterone arm and placebo arm respectively [hazard ratio (HR) for death =0.62, 95% confidence interval (CI): 0.51–0.76, P<0.001]. Median PFS was 33 *vs.* 14.8 months in the Abiraterone arm and placebo arm respectively (HR 0.47, 95% CI: 0.39–0.55, P<0.001 (27). A final analysis at median follow up of 51.8 months confirmed Abiraterone's superiority over ADT alone. Median OS was significantly longer in the Abiraterone *vs.* placebo arm (53.3 *vs.* 36.5 months; HR 0.66,

95% CI: 0.56–0.78, $P < 0.0001$) (35). In the Abiraterone group, 16% of patients discontinued treatment due to adverse effects as compared to 10% in the placebo group. The most common grade 3–4 adverse effects in the Abiraterone group were hypertension (21% of patients), hypokalaemia (12%) and liver transaminase increase (5%).

The STAMPEDE trial group also incorporated an arm comparing Abiraterone plus prednisone to ADT. 1,917 men with hormone-sensitive prostate cancer were randomised to receive ADT with or without Abiraterone 1,000 mg daily plus prednisone 5 mg daily. In both arms, median age of men was 67 years and 78% of men had WHO performance status of 0. Metastatic disease patients occupied approximately 50% of both arms. Of these patients, 88% of men had bone metastases and over 95% were newly diagnosed cancer. At median follow up of 40 months, the Abiraterone group showed an improved 3-year survival rate of 83% compared to 76% in the ADT only group (HR for death = 0.63, 95% CI: 0.52–0.76, $P < 0.01$). In the subgroup analysis of mHSPC patients only, Abiraterone again demonstrated improved 3 year OS (HR 0.61, 95% CI: 0.49–0.75, $P < 0.001$) and improved 3 year PFS (HR 0.40, 95% CI: 0.34 to 0.47, $P < 0.001$) (36). Grade 3–4 adverse effects were reported in 47% of the Abiraterone group compared to 33% in the ADT only group. The most common adverse effects in the Abiraterone group were endocrine disorders (14%), musculoskeletal disorders (7%), increased hepatic transaminases (7%), hypertension (5%) and gastro-intestinal disorders (5%).

In regards to adverse effects, pooled analysis of results from the STAMPEDE trial and LATITUDE trial showed that Abiraterone exhibited an approximately three fold increase in grade 3–4 acute cardiac and hepatic toxicity and a two fold increase in grade 3–4 vascular events relating to hypertension (37). Abiraterone therefore should be prescribed with caution or close follow up in patients with pre-existing hypertension, cardiac disease and liver disease. Clinicians should also be mindful of diabetic patients as Abiraterone needs to be taken in combination with prednisone.

Enzalutamide plus ADT

ENZAMET was an international, open label, randomised, phase 3 trial of 1,125 men with mHSPC. These men were randomised in 1:1 ratio to either receive Enzalutamide 160 mg daily or a standard care nonsteroidal drug (bicalutamide, nilutamide or flutamide) with background continuous

testosterone suppression. Median age of men in both arms was 69 years. 52% of men in the Enzalutamide arm had high volume disease as compared to 53% in the standard of care arm. Docetaxel was given to 17% and 15% of the Enzalutamide group and standard care group respectively. At a median follow up of 34 months, there were 102 deaths *vs.* 134 deaths in the Enzalutamide arm and standard of care arm respectively (HR for death 0.67, 95% CI: 0.52–0.86, $P = 0.002$). The trial was not yet able to state median survival time. 3-year OS rates were estimated to be 80% and 72% in Enzalutamide group *vs.* standard care group respectively. PSA PFS rates were 67% *vs.* 37% in the Enzalutamide group *vs.* standard care group respectively (HR 0.39, 95% CI: 0.33–0.47, $P < 0.001$). Clinical PFS rates were 68% and 41% in Enzalutamide group *vs.* standard care group respectively (HR 0.40, 95% CI: 0.33–0.49, $P < 0.001$). Interestingly, subgroup analysis of men with high volume disease (HR 0.74, 95% CI: 0.55–1.01, $P = 0.04$), and planned early Docetaxel treatment (HR 0.91, 95% CI: 0.62–1.35, $P = 0.04$) found that Enzalutamide's effect on OS was less pronounced (38). Approximately 6% of patients in the Enzalutamide arm discontinued treatment due to adverse effects compared to 3% in the standard of care arm. Febrile neutropenia (7%), hypertension (8%), fatigue (6%), and syncope (4%) were the most common grade 3–5 adverse effects recorded. Of note, all but two events of febrile neutropenia occurred during early Docetaxel treatment and also only 2 events of seizures was recorded (38).

ARCHES trial was an international, randomised, phase 3 trial that randomised 1,150 men with mHSPC in a 1:1 ratio to either Enzalutamide or placebo with ADT. Overall, the median age of these men was 70 years and over 75% of the men had ECOG performance status of 0. 63.2% of these men had high volume disease and 17.9% had received prior Docetaxel chemotherapy. These characteristics were well balanced between the two study groups. Preliminary results at median follow up of 14.4 months have shown Enzalutamide reduced risk of radiographic disease progression or death by 61% compared to the placebo arm (HR 0.39, 95% CI: 0.30–0.50, $P < 0.001$). Median radiographic PFS was not reached with Enzalutamide *vs.* 19 months for the placebo group. Subgroup analysis of high and low volume disease and patients with prior Docetaxel treatment showed similar results across all groups. OS statistics are not yet mature (39). Discontinuation of Enzalutamide due to adverse effects occurred in 7% of patients compared to 5% in the placebo group. Grade 3 or above adverse effects recorded included hypertension (3%), fatigue (1.6%),

musculoskeletal events (1.6%) and convulsions (0.3%).

Apalutamide plus ADT

The TITAN trial remains the only study analysing Apalutamide in the mHSPC setting. 1,052 men were recruited then assigned to either receive ADT plus Apalutamide or placebo. This cohort of men had a median age of 68 years; 11% of men had received previous Docetaxel and 16.4% of patients previous prostatectomy or radiotherapy for localised disease. 63% of men had high volume disease and the remainder had low volume disease. At median follow up of 22.7 months, the OS percentage was greater in the Apalutamide arm (82% *vs.* 74%; HR for death 0.67, 95% CI: 0.51–0.89, $P=0.005$) and there was no significant difference in this result when analysing according to disease volume. Apalutamide also performed better when assessing for radiographic PFS (68% *vs.* 48%; HR for radiographic progression or death 0.48, 95% CI: 0.39–0.60, $P<0.001$) (40). Adverse effects led to discontinuation of Apalutamide in 8% of patients compared to 5% in the placebo group. Grade 3 or above fatigue (1.9%) and rash (2.7%) were noticeably higher in the Apalutamide group compared to the placebo group. Grade 1–2 hypothyroidism (6.5%) was also noticeably increased in the Apalutamide arm (41).

Treatment choice

Four agents have now demonstrated OS and PFS benefits in patients with mHSPC. A recent meta-analysis of the above trials attempted to indirectly compare the efficacy of each combination approach however found no statistically significant differences in OS (41). Therefore, these practice changing results have now given clinicians several treatment options for mHSPC.

For now, treatment selection should be tailored to each individual case with differing adverse effect profiles of each medication at the forefront of management considerations. These are based on the reported rates of adverse effects from the trials above. In essence, patients with poorly controlled heart disease, diabetes, hypertension or liver disease should not be offered Abiraterone. Patients who have had a major stroke, moderate-severe cognitive issues or seizures should not be offered enzalutamide. And when considering taxane based chemotherapy, contraindications include poor performance status neuropathy, dementia, uncontrolled pre-existing serious disease, severe hepatic or renal insufficiency and neutropenia (42). Thought should

also be given to patient lifestyle and housing location when deciding between frequent hospital visits for intravenous chemotherapy or daily oral ARPIs.

Another key consideration centres around the impact of choice of initial therapy for mHSPC on subsequent treatment selection in mCRPC. A logical approach would be to use docetaxel following prior ARPI therapy, and vice versa. Whether any mHSPC patients would benefit from switching to a second-line ARPI at time of progression to mCRPC is unknown, although currently available data suggests this would be of limited value (43,44). With additional systemic agents likely to enter the treatment paradigm for mCRPC and mHSPC in coming years, carefully designed prospective clinical trials and high-quality real-world databases will be needed to help address questions around treatment sequencing.

Similarly, the role of combination chemotherapy and ARPIs requires further investigation. Currently, there is no data to support concurrent treatment with docetaxel and an ARPI. In fact, in ENZAMET triplet therapy (ADT + Docetaxel + Enzalutamide) appeared to be associated with higher rates of adverse events including neuropathy (38). It must be said however that ENZAMET was not designed to formally assess the combination of Docetaxel and Enzalutamide. Two ongoing trials are assessing the combination of Docetaxel and an ARPI, namely ARASENS (Docetaxel +/- Darolutamide—NCT02799602) (45) and PEACE-1 (Docetaxel +/- Abiraterone—NCT01957436). The results of these trials are eagerly awaited and will help to define the benefit, if any, of concurrent treatment with Docetaxel and an ARPI in mHSPC.

Additionally, there have been some indications that volume of disease, age and cost effectiveness could have a role to play in stratifying patients for each drug. However, definitions for volume and age need to be standardised and further investigated and costs will most likely change in the coming years. Furthermore, the impact of novel imaging using prostate specific membrane antigen (PSMA) is not yet established. Although PSMA PET/CT is superior to CT and bone scan for the evaluation of metastases in newly diagnosed patients (46) which may lead to stage migration of mHSPC patients, it is not yet clear if this will lead to improved oncological outcomes (47). Certainly, nuclear medicine physicians now play a pivotal role in the prostate cancer multidisciplinary team (48).

The role of the urologist

Management of mHSPC has traditionally been in the

domain of the urologist. Since ADT was standardised as a first-line option for these patients many years ago, it has been the urologist who has been the primary specialist overseeing their care until the emergence of castration-resistance. However, the upfront use of Docetaxel chemotherapy and ARPIs has led to changes in patterns of care, with medical oncologists playing an increasing role in the primary management of mHSPC. Whilst Docetaxel is most often administered by medical oncologists, it is also administered by urologists in some countries, especially in the Asia-Pacific region (2). The increasing role for well tolerated oral ARPIs combined with ADT for mHSPC, also means that urologists can continue to play a key role in the management of mHSPC, provided they are willing to become facile with the safe use and monitoring of these agents (49). Ultimately, these patients are best managed in multidisciplinary teams, taking into account patient and disease factors, as well as access and affordability issues (50).

Nursing considerations

With a number of treatments now available for men with metastatic prostate cancer, the role of a nurse is vital in the ongoing coordination and management of patient care and the improvement of quality of life (51). Nurses have the ability to develop relationships with the patient and their families whilst also creating support networks tailored to the individual's lifestyle and preferences (52). Information relating to age, comorbidities, past experiences, reliability and financial status can then be available for clinicians to consider when decision-making regarding appropriate treatment (51,53). This information also leads to early identification of referrals to allied health, culminating in improved patient tolerability of treatment and ultimately resulting in greater quality of life and overall experience (53). Although studies have shown patients benefit from the involvement of nursing coordination, health organisations still inconsistently utilise this resource. Further research and standardisation of nursing care is required to maximise its role in prostate cancer survivorship (51).

Cost

The financial burden of advanced prostate cancer can have a significant impact on cancer survivorship (54). Although Abiraterone and Enzalutamide have now demonstrated an improved survival benefit, Docetaxel remains the more cost effective option. This was confirmed in a statistical analysis

by Sathianathen *et al.* who showed in a cohort of men from the US, ADT plus Abiraterone demonstrated clinically better results compared to ADT plus Docetaxel but conversely ADT plus Docetaxel was the more cost-effective treatment option (55). Moving forward, reimbursement status and affordability of these drugs will change as evidence for them grows larger. Nevertheless, a holistic approach should be implemented when discussing the correct treatment plan for each patient.

Other approaches

Treatment of the primary tumour

The last decade has seen much debate amongst prostate cancer specialists in regard to cytoreductive treatment for the primary tumour. Two large trials have revealed answers pertaining to external beam radiotherapy (EBRT) in this space, however, the specific cohorts of patients that would benefit from ERBT and the field of ERBT used should be further refined. Furthermore, studies comparing cytoreductive prostatectomy to standard treatment need to be carried out.

The evidence for ERBT to the primary tumour is primarily derived from the STAMPEDE trial and HORRAD trial with results from the PEACE-1 trial (56) eagerly awaited. The HORRAD trial recruited 432 men with PSA >20 ng/mL and primary bone metastases on whole body bone scan. These men were randomised to receive ADT with or without ERBT (only prostate and any extra-prostatic tumour extension were targeted, pelvic lymph nodes were not). With median follow up of 47 months, improvement in OS was not shown with added ERBT. However in a subgroup analysis of patients with low metastatic burden (<5 metastases), radiotherapy resulted in a non-significant improvement in OS (HR 0.68, 95% CI: 0.42–1.10) (57). The STAMPEDE trial randomised 2061 men with newly diagnosed mHSPC to receive standard therapy (ADT +/- Docetaxel) with or without ERBT (prostate only). Around 60% of these men had high metastatic burden. Results showed that for all patients, failure free survival was improved but not OS. However, failure free survival (HR 0.59, 95% CI: 0.49–0.72, $P < 0.0001$) and OS (HR 0.68, 95% CI: 0.52–0.90, $P = 0.007$) were both improved specifically for patients with low metastatic burden (<4 bone metastases and no visceral metastases) (58).

In regards to the analysis of the low metastatic burden cohorts in both trials, the similar effect size but lack of

statistical significance in the HORRAD trial indicates the HORRAD trial was underpowered to show significant difference in this subgroup analysis. At a recent Advanced Prostate Cancer Consensus Conference (APCCC), 98% of panellists agreed that based on the current literature, local treatment of the primary tumour has an OS benefit only in patients with newly diagnosed, low-volume/low-burden mHSPC (50).

Theranostics

Within the field of theranostics, radioligand therapy has seen much development in the last 5 years. This technology builds on the discovery of the pivotal prostate specific membrane antigen (PSMA) found on prostate cancer cells. Radioligand therapy utilises PSMA as a vehicle for the radiometal ¹⁷⁷Lutetium to penetrate cancer cells and emit energy leading to cell death (59). So far, ¹⁷⁷Lutetium PSMA-617 has only seen viable results in the mCRPC setting (60,61). The transition of ¹⁷⁷Lutetium PSMA-617 to mHSPC patients is the aim of the UpFrontPSMA trial in Australia (62). The trial is currently in the recruitment phase with the aim of including 140 patients in a randomised phase 2 trial of Docetaxel with or without ¹⁷⁷Lutetium PSMA-617 in hormone naïve prostate cancer. Their primary objective will be PSA response but will have secondary endpoints analysing PFS (PSA and radiological), time to castration resistance, quality of life and OS.

Conclusions

Prostate cancer specialists are now armed with several agents that can be utilised for newly diagnosed mHSPC. Docetaxel, Abiraterone, Enzalutamide and Apalutamide have all been proven in large randomised trials to prolong OS compared to previous standard of care ADT. As these new agents become more readily available and subsidised, clinicians should dictate their choice of treatment based on patient preference, co-morbidities, and medication adverse effect profiles. Furthermore, the role of a clinical nurse is important in this decision and can improve patient survivorship.

Along with these novel medications, other approaches including treatment to the primary tumour, and radioligand therapy are currently being investigated for mHSPC. The combination of these therapies will look to push the envelope for advanced prostate cancer treatment and survival.

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