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TOPIC PAPER

Current status and future perspectives of the managements of metastatic hormone-sensitive prostate cancer

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Abstract

Purpose The therapeutic landscape for metastatic hormone-sensitive prostate cancer (mHSPC) has changed dramatically. Here, we provide the current status and future prospective of the management of mHSPC.

Methods We reviewed recent literature of landmark studies on the managements of mHSPC.

Results Upfront docetaxel or androgen receptor signaling inhibitor (ARSi) in addition to ADT has improved survival in mHSPC patients and has become the new standard of care. Triplet therapy with docetaxel, ARSi and ADT also improved survival. In the future, triplet therapy may become the standard of care. Oligometastatic mHSPC patients could benefit from local therapy. The inclusion of risk factors or the genetic biomarkers will provide the best treatment for individual mHSPC patients.

Conclusion Strong systemic therapy in the first-line treatment of mHSPC has been shown to improve survival and quality of life. Currently, several clinical trials are evaluating novel compounds such as PARP inhibitor, AKT inhibitor, and immune checkpoint inhibitor. The therapeutic landscape of mHSPC management will change dramatically.

Keywords Metastatic hormone-sensitive prostate cancer · Docetaxel · Abiraterone · Enzalutamide · Apalutamide · Darolutamide

Introduction

In the United States, the incidence of metastatic prostate cancer has increased and the incidence of metastatic prostate cancer is projected to increase in the future. In 1941, Charles Huggins proved that bilateral orchiectomy reduced tumor volume and improved symptoms of prostate cancer [1]. Androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone (LHRH) agonists (leuprolide and goserelin) or antagonists (degarelix), receptor antagonists, or bilateral orchiectomy is the standard treatment for men with metastatic hormone-sensitive prostate cancer (mHSPC). Recently, oral LHRH receptor antagonists (relugolix) have been developed, which may be easier to use. The response rate to ADT is 60–80% at 2 years, and the response is not permanent, with the majority of patients acquiring androgen insensitivity within 2 years [2]. The time to castration-resistant prostate cancer (CRPC) has been shown to affect survival. The 5-year relative survival rate of mHSPC is 30%, and the median survival time of mCRPC is approximately 3 years [3]. For this reason, clinical trials were initiated in an attempt to prolong the hormone-sensitive period and reduce side effects that affect the quality of life (QOL). Combined androgen blockade (CAB) therapy, which adds a first-generation antiandrogen to ADT, was reported in 1982 [4]. Several randomized trials in patients with advanced prostate cancer showed only a 2–3% improvement in 5-year survival and no difference in overall survival (OS) in response to CAB therapy [5]. However, due to the side effects and small survival benefit of CAB, it is not recommended as the standard therapy for mHSPC. Recently, the addition of docetaxel chemotherapy and second-generation antiandrogens to ADT

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has been demonstrated to improve OS and has become the new standard of care. We reviewed the current approaches in the management of mHSPC (Table 1) (Fig. 1).

Docetaxel

Combination therapy with ADT and docetaxel became the standard of care for mHSPC in 2015 based on the results of three phase III trials. Stratification by metastatic disease volume was performed in the CHAARTED trial, with high volume defined as lesions with visceral metastases or more than four bone metastases (at least one bone other than vertebral or pelvic bone) [6]. In the first reported GETUG-AFU 15 trials, 385 patients with mHSPC were randomized to receive ADT with or without docetaxel for up to nine cycles. No significant difference was found in OS (hazard ration (HR) 1.01, 95% confidence interval (CI) 0.75–1.36) [7]. Long-term survival analysis of the GETUG-AFU trial showed that docetaxel did not improve OS in patients with de novo metastases, high volume or low volume (HR 0.88, 95% CI 0.68–1.14, $p=0.3$) [8]. Patient groups in the GETUG-AFU were characterized by a low grade in about half of the patients and low volume in more than three-quarters. In the CHAARTED trial, 790 patients with mHSPC were randomized to receive six cycles of docetaxel plus ADT or ADT alone. The results showed an OS prolongation of 13.6 months (HR 0.61, 95% CI 0.47–0.80, $p=0.0018$)

Table 1 Characteristics of the studies for mHSPC

Study	Intervention	Docetaxel Use (%)	De novo M1 (%)	PFS (HR; 95% CI)	OS (HR; 95% CI)	High-volume OS (HR; 95% CI)	Low-volume OS (HR; 95% CI)
CHAARTED	ADT+docetaxel vs ADT	0	73	0.62; 0.51–0.75	0.72; 0.59–0.89	0.63; 0.50–0.79	1.04; 0.70–1.55
STAMPED (ARM C)	ADT+docetaxel vs ADT	0	95	0.69; 0.59–0.81	0.81; 0.69–0.95	0.81; 0.64–1.02	0.76; 0.54–1.07
GETUG-AFU15	ADT+docetaxel vs ADT	0	67	0.75; 0.58–0.97	0.88; 0.68–1.14	0.78; 0.56–1.09	1.02; 0.67–1.55
LATTITUDE	ADT+abiraterone vs ADT	0	100	0.47; 0.39–0.55	0.66; 0.56–0.78	0.62; 0.52–0.74	0.72; 0.47–1.10
STAMPED (ARM G)	ADT+abiraterone vs ADT	0	97	0.31; 0.26–0.37	0.61; 0.49–0.75	0.60; 0.45–0.78	0.64; 0.42–0.97
ARCHEZ	ADT+enzalutamide vs ADT	18	77	0.38; 0.31–0.46	0.66; 0.53–0.81	0.66; 0.52–0.83	0.66; 0.43–1.03
ENZAMET	ADT+enzalutamide vs CAB	45	58	0.40; 0.33–0.49	0.67; 0.52–0.86	0.80; 0.59–1.07	0.43; 0.26–0.72
TITAN	ADT+apalutamide vs ADT	11	86	0.34; 0.29–0.41	0.65; 0.53–0.79	0.70; 0.56–0.88	0.52; 0.35–0.79
ARASENS	ADT+darolutamide + Docetaxel vs ADT	0	86	0.36; 0.30–0.42	0.68; 0.57–0.80	–	–

ADT androgen-deprivation therapy, *CAB*, combined androgen blockade, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ration, *CI* confidence interval

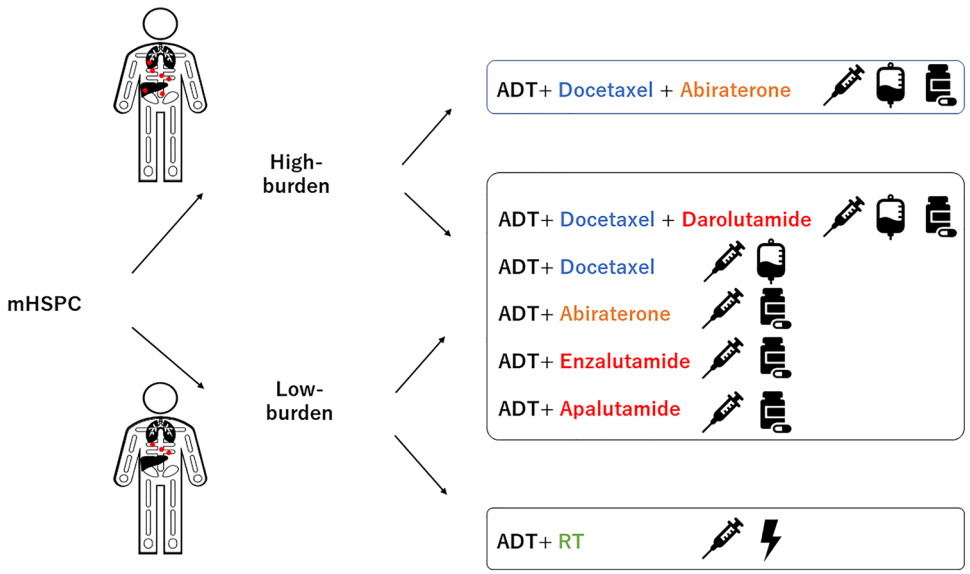

Fig. 1 Strategy for mHSPC based on the tumor burden. *ADT* androgen-deprivation therapy, *mHSPC* metastatic hormone-sensitive prostate cancer, *RT* radiation therapy.

[6]. Long-term survival analysis of the CHAARTED trial showed an improvement of OS in the docetaxel group (HR 0.72, 95% CI 0.59–0.89, $p=0.0018$). Compared to high-volume patients, no significant difference in OS was observed in low-volume or locally treated patients. The characteristics of the patients, of which 65% were high-volume, would have influenced the overall results [9]. In the C arm of the STAMPEDE trial with 37% non-metastatic (M0) patients, ADT maintained with six cycles of docetaxel and prednisolone 10 mg/day prolonged OS by 10 months compared with ADT alone (HR 0.78, 95% CI 0.66–0.93, $p=0.006$) [10]. Additional analysis for patients with mHSPC in the C arm showed that upfront docetaxel prolonged OS by 16 months compared with ADT alone (HR 0.81, 95% CI 0.69–0.95, $p=0.009$). There were no significant differences between high- and low-volume patients [11]. Comparing the three trials, the CHAARTED trial performed best. A subgroup analysis of the combined CHAARTED and GETUG-AFU 15 trials showed that high-volume patients benefited more than low-volume patients. Based on these results, docetaxel came to be preferred in high-volume patients as the 1st line treatment. This subgroup analysis did not directly compare de novo and recurrent diseases but did not show OS significance [12]. Docetaxel carries a high risk of developing febrile neutropenia (FN). Three major clinical trials showed that FN appeared in 6–15% of patients and 17–23% failed to complete up to six cycles. Upfront docetaxel reported statistically significant lower FACT-P scores at 3 months but significantly higher FACT-P scores at 12 months compared with ADT only [13].

Androgen receptor signaling inhibitor (ARSi)

Abiraterone acetate

Two clinical trials were reported in 2018, showing the efficacy of ARSi for mHSPC. In the LATITUDE trial, high-risk was defined as having two of three high-risk prognostic factors (Gleason score of 8 or higher, three or more bone lesions, or visceral metastases). A total of 1199 patients with high-risk mHSPC were randomized to receive ADT with abiraterone plus prednisolone 5 mg/day or ADT alone. The results showed a significant improvement of OS in the abiraterone group (HR 0.62, 95% CI 0.51–0.76, $p<0.0001$) [14]. Long-term survival analysis showed that the median OS was increased by 13.6 months in the abiraterone group. Post hoc analysis stratified by disease volume as used in the CHAARTED trial showed that low-volume patients did not show a significant difference in OS compared with high-volume patients [15]. Arm G of the STAMPEDE trial, similar in design to the LATITUDE trial, showed prolonged OS in patients with hormone-sensitive prostate cancer treated with ADT with abiraterone plus prednisolone 5 mg/day or ADT alone (HR 0.63, 95% CI 0.52–0.76, $P<0.001$). In the STAMPEDE trial, 48% of the patients included were M0, and additional analyses were performed in patients with mHSPC. 1002 patients with mHSPC showed a prolonged OS compared with those with ADT alone (HR 0.61, 95% CI 0.49–0.75). Efficacy was demonstrated regardless of the lesion volume or risk [16]. Based on these results, abiraterone was strongly recommended for patients with high-risk mHSPC. Both trials showed that abiraterone was effective in the absence of prior docetaxel therapy. All patients in the LATITUDE trial and 97% of Arm G M1 patients in the STAMPEDE trial had de novo metastases. Efficacy of upfront abiraterone in patients with recurrent mHSPC disease was not clear. Adverse events such as cardiovascular disorder, hypokalemia, and hepatic disorder were higher within the first 3 months of treatment in upfront abiraterone group. Findings from FACT-P scores suggested an improved QOL with upfront abiraterone compared with ADT only [15].

Enzalutamide

Two clinical trials of upfront enzalutamide for mHSPC were reported in 2019, namely the ARCHES and ENZAMET trials, in which patients were stratified by disease volume and docetaxel use. In the ARCHES trial, 1150 patients with mHSPC were randomized to receive ADT with or without enzalutamide. Upfront enzalutamide improved progression-free survival (PFS) in patients with mHSPC (HR 0.39, 95% CI 0.30–0.50), but no significant differences in OS were observed at a median follow-up of 1.2 years [17]. The final survival analysis showed improved OS in the enzalutamide group (HR 0.66, 95% CI 0.53–0.81, $p<0.001$). Furthermore, upfront enzalutamide showed efficacy regardless of disease volume or prior docetaxel treatment [18]. In the ENZAMET trial, 1125 patients with mHSPC were randomized to receive enzalutamide plus ADT or CAB. Enzalutamide plus ADT improved OS (HR 0.67, 95% CI 0.52–0.86, $p=0.002$). Subgroup analysis showed that OS was less improved in the enzalutamide group in patients previously treated with docetaxel and high disease volume [19]. Further long-term follow-up results are awaited since the number of deaths was too small to reach a definitive conclusion. Regarding the timing of docetaxel therapy, the ARCHES trial included an entire group of patients who received docetaxel prior to enzalutamide, whereas the ENZAMET trial included those receiving concomitant therapy. It is not known if the timing of docetaxel contributes to OS, but this needs to be examined in the future. Since enzalutamide increased the risk of seizures in CRPC clinical trials, patients with a history of seizures were excluded from mHSPC clinical trials. However, the ARCHES and the ENZAMET trials of mHSPC did not

show an increased risk of seizures. Based on the increased risk of developing peripheral neuropathy in the ENZAMET trial, patients with a history of neuropathy should avoid concomitant use of enzalutamide and docetaxel.

Apalutamide

A clinical trial using apalutamide for mHSPC, the TITAN trial, was reported in 2019, in which 1,052 patients with mHSPC were randomized to receive ADT with or without apalutamide. Upfront apalutamide improved OS at a median follow-up of 2 years (HR 0.67, 95% CI 0.51–0.89, $p=0.005$) [20]. The final survival analysis showed improved OS in the apalutamide group (HR 0.65, 95% CI 0.53–0.79, $p<0.0001$) [21]. Efficacy of upfront apalutamide was demonstrated regardless of metastatic disease volume. However, patients previously treated with docetaxel did not show improved OS. Apalutamide carries a high risk of skin rash and hypothyroidism. Particularly, skin rash can be severe and the optimal management with anti-histamine and corticosteroids should be provided.

ARSi+ docetaxel

Abiraterone+ docetaxel

In the PEACE-1 trial of triple therapy for mHSPC, a total of 1173 patients with mHSPC were randomized to standard therapy (ADT−/+ docetaxel), standard therapy plus abiraterone, standard therapy plus radiation therapy (RT), or standard therapy plus abiraterone plus RT. No blinding of physicians or patients was performed after the assignment. Of the 710 patients treated with docetaxel, 355 received ADT+ docetaxel (-/+ RT) and 355 received ADT+ docetaxel+ abiraterone (−/+ RT). All patients had de novo metastases, and docetaxel and abiraterone were started concurrently. Abiraterone was combined with prednisolone 10 mg/day. OS was better in the abiraterone group than in the no-abiraterone group (HR 0.82, 95% CI 0.69–0.98, $p=0.030$). Among patients treated with docetaxel, OS was better in the abiraterone combination group (HR 0.75, 95% CI 0.59–0.95, $p=0.017$). RT to the prostate did not affect OS. Stratification by lesion volume was performed, and patients with high volume showed significantly improved OS, while patients with low volume did not. Triple therapy may become the standard of care in high-volume patients. However, triple therapy slightly increased hypertension [22].

Darolutamide+ docetaxel

In the ARASENS trial, 1306 patients with mHSPC were randomized to receive darolutamide plus ADT plus docetaxel or ADT plus docetaxel, stratified by disease volume and alkaline phosphatase levels (ALP). The darolutamide group showed a significant improvement in OS compared with the ADT plus docetaxel group (HR 0.68, 95% CI 0.57–0.80, $p<0.0001$) [23]. With de novo metastases accounting for 86.1% of the total population, the efficacy of darolutamide plus ADT plus docetaxel for patients with recurrent mHSPC was not clear, but the efficacy of the triplet was shown in de novo disease. Side effects did not differ between the two groups except for rash and hypertension, proving that darolutamide did not add to the toxicity of ADT plus docetaxel.

Local treatment

Two-phase III trials were reported on the efficacy of the combination of ADT and external beam radiotherapy (EBRT) to the prostate in mHSPC. In the HORRAD trial, 432 mHSPC patients with bone metastases were randomized to ADT with or without EBRT. Survival analysis showed no improvement of OS in the EBRT group (HR 0.90, 95% CI 0.70–1.14) [24]. Subgroup analysis showed a significant improvement in OS in patients with less than five bone metastases (HR 0.68, 95% CI 0.42–1.10). In the STAMPEDE Arm H trial, 2061 patients with mHSPC bone metastases were randomized to ADT with or without EBRT. Patients receiving prior docetaxel treatment were included. Survival analysis showed no improvement of OS in EBRT group (HR 0.92, 95% CI 0.80–1.06, $p=0.266$) [25]. However, subgroup analysis showed a significant improvement of OS in low-volume patients (HR 0.68, 95% CI 0.52–0.90). In both trials, all patients had de novo metastases and irradiation of the prostate was within the effective dose. In a pooled analysis of the two trials, there was no significant difference in OS (HR 0.92, 95% CI 0.81–1.04, $p=0.195$), but a significant improvement in OS in patients with < 5 bone metastases (HR 0.73, 95% CI 0.58–0.92, $p<0.01$) [26]. EBRT was well tolerated in combination therapy, with no difference in AEs. The role of cytoreductive radical prostatectomy is unproven. Trials of the g-RAMMP (NCT02454543) and the TROMBONE (SRCTN15704862) for local treatment by surgery in low-volume mHSPC are ongoing. The efficacy of metastasis-directed therapy (MDT) for mHSPC is not clear, and clinical trials are ongoing.

Genetic biomarkers

Since the treatment options for metastatic prostate cancer have increased, the development of biomarkers for selecting patients who benefit to ARSis or docetaxel is desired. Circulating tumor cell (CTC) and circulating tumor DNA (ctDNA) are gaining attention as non-invasive biomarkers to analyze the tumor characteristics. CTC counts and ctDNA levels have been reported as validated prognostic

factors for mHSPC and mCRPC. However, not all patients have detectable ctDNA levels and may give false- negative results. Systemic treatments rapidly reduce CTC and ctDNA from the systemic circulations and they may serve as valid predictor of efficacy. Advanced tumors of the prostate can harbor mutations in the homologous recombinant repair (HRR) gene, which destabilize the genome, resulting in a worse prognosis compared to patients without mutations. It is not clear whether HRR mutations affect the prognosis of mHSPC. Several trials of the PARP inhibitors talazoparib and niraparib and olaparib—the PARP inhibitors that has already approval for mCRPC—in combination with ARSi are ongoing in mHSPC patients with HRR mutations. Loss of function of tumor suppressor genes such as *TP53*, *PTEN*, *RB1*, and *SPOP* may be associated with the prognosis of mCRPC. The relationship of mHSPC with tumor suppressor genes is under investigation. Genetic alterations of AR in CRPC are present in approximately 90% of cases [27]. The presence of AR splice variant 7 (AR-V7), which lacks a binding site, confers resistance to ARSi in mCRPC. The presence of AR-V7 has rarely been detected in mHSPC and cannot be a prognostic factor [28].

Recently, mRNA profiling as well as DNA sequencing has received much attention. Transcriptome profiling from tissues of patients with mHSPC enrolled in the CHAARTED trial was reported. The luminal B subtype prolonged OS upon docetaxel treatment (HR 0.45, $p = 0.007$) [29]. The basal subtype had a greater effect on PFS than the luminal subtype in the TITAN trial [30]. Gene expression classification may be recommended to determine the optional treatment for mHSPC patients. Trial of capivasertib (NCT04493853), an AKT inhibitor, and pembrolizumab (NCT04191096), a PD-1 inhibitor, in combination with ARSi in *PTEN*-deficient mHSPC patients is ongoing. Biomarker-driven clinical trials, the development of new standard therapies for genetic abnormalities, and new epigenomic analyses will be needed.

Conclusion

Upfront docetaxel or ARSi improved survival in patients with mHSPC. Triplet therapy with docetaxel, ARSi and ADT also improved survival. The optimal treatment for mHSPC patients with low- and high-volume diseases should be selected based on biomarkers. Several clinical trials are currently underway, including studies of PARP inhibitors, AKT inhibitors, and immune checkpoint inhibitors. In the near future, the therapeutic landscape of mHSPC management is expected to change dramatically.

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Declarations

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Informed consent This article does not contain any studies with human participants. Therefore, issues of informed consent are not applicable.

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