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Professional Paper

A NEW PARADIGM IN THE SYSTEMIC TREATMENT OF ADVANCED PROSTATE CANCER: THE EARLIER THE BETTER OR THE MORE THE BETTER

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SUMMARY – Androgen deprivation therapy (ADT) has been the backbone of treatment for advanced prostate cancer (APC) for decades. The introduction of docetaxel and androgen receptor pathway inhibitors (ARPI; abiraterone, enzalutamide, apalutamide) in the treatment of metastatic hormone-sensitive PC (mHSPC) has changed the treatment landscape of APC. Data from studies with docetaxel (CHAARTED, STAMPEDE) and NHT (STAMPEDE, LATITUDE, ENZAMET, ARCHES, TITAN) suggest that ADT monotherapy is no longer acceptable for the treatment of men with mHSPC. Systemic treatment options in this indication include: doublet therapy consisting of ADT plus abiraterone (AAP) or apalutamide (APA), or enzalutamide (ENZ); ADT plus docetaxel remains an option for settings where ARPI is not available or the combination of ADT and docetaxel with ARPI is not possible, and triple therapy consisting of a combination of ADT, docetaxel, and AAP or darolutamide (PEACE-1, ARASENS studies), especially for patients with high-risk/high-volume synchronous disease. More data are needed on the potential combination of ADT with docetaxel and APA or ENZ. In the decision to treat a patient with mHSPC, in addition to the results of relevant studies, the general condition of the patient, their comorbidities and co-medication, affinities, availability and toxicity of drugs, and the cost of treatment should all be taken into account. Finally, further elucidation of the biology of different groups of mHSPC to identify different clinical behavior may be helpful in deciding the optimal treatment of these patients. Analysis of transcriptomic biomarkers of patient samples from large, practice-changing mHSPC studies could optimize patient selection for different treatment strategies and help physicians make decisions in daily practice.

Key words: *hormone-sensitive prostate cancer; docetaxel; androgen receptor pathway inhibitors; doublet therapy; triplet therapy*

Introduction

Androgen deprivation therapy (ADT) has been the backbone of the treatment of advanced prostate cancer (APC) for decades[1]. It involves the use of gonadotrophin-releasing hormone (GnRH) agonists or antagonists or surgical castration (i.e. orchiectomy), which directly suppresses testosterone. Intermittent ADT (a concept developed to minimize quality of life detriments associated with continuous ADT) or the addition of first-generation antiandrogens (e.g. flutamide, bicalutamide) leading to complete androgen blockade have been tried in order to improve outcomes in patients with advanced disease[2,3]. However, despite attempts to improve the efficiency of ADT among patients with metastatic PC, the median duration of sensitivity to ADT is usually 2-3 years, and resistance to

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ADT inevitably occurs in most patients[4]. With a better understanding of the role of the androgen receptor signaling pathway in the progression of PC and with the arrival of androgen receptor pathway inhibitors (ARPI), the overall survival (OS) of patients with APC has been improved significantly[4,5]. Since 2005, multiple new therapies for metastatic castrate-resistant PC (mCRPC) have emerged that are now considered the standard of care. Namely, docetaxel, cabazitaxel, sipuleucel-T, abiraterone acetate (AA), enzalutamide (ENZ), and radium-223 gained Food and Drug Administration (FDA) approval on merits of OS benefit in the first or second-line of treatment of mCRPC[6-13]. Despite proven advancements in treatment for mCRPC, sequential survival gain from these agents only ranged from 2.5-4.5 months[6-13]. Most patients receiving these drugs experienced disease progression, mainly during ADT for metastatic hormone-sensitive disease. Therefore, it was reasonable to consider whether these agents administered in an earlier phase (hormonally sensitive) would delay the development of castration resistance and potentially further prolong the survival of these patients. The profile of patients who receive ADT for mHSPC is different, and knowing it is thus essential for choosing the optimal therapy: most of them present with *de novo* (i.e. synchronous) metastatic disease (these patients have a more aggressive disease course of shorter duration of hormonal sensitivity and worse OS), while the others progress following prior local therapy (radical prostatectomy or radiotherapy with curative intent) (i.e. metachronous or primary progressive disease)[14,15]. Prospective trials have shed light on the prognostic and predictive role of disease burden assessed by conventional imaging[16,17] (**Table 1**). Furthermore, these patients could be fit and young or old and frail. Lastly, some patients have received ADT with radiotherapy or after prostatectomy for biochemical failure. Over the last eight years, trials of novel agents used for mHSPC have radically transformed the treatment landscape in this space. We now have accurate data for the OS benefit of docetaxel or ARPI such as AA, ENZ, or apalutamide (APA) when they have been added to the ADT backbone in this setting[17-23] (**Table 2**). All these approaches have shown how to improve survival substantially, but they have also provided new clues to previously undefined biology. The most obvious point is the marked difference in the benefit of these agents used in the mHSPC setting compared with patients with mCRPC. It has become clear that patients with hormone-sensitive diseases benefit substantially more. In addition, the approval of three ARPI within the last four years for the treatment of mHSPC makes treatment choices and therapy sequencing more complex. Standard-of-care first-line therapy now includes ADT plus docetaxel or an ARPI rather than ADT alone. Additional treatment intensification, i.e. triplet therapy (a combination of ADT, docetaxel, and an ARPI), could further improve the treatment outcomes of a subset of patients with mHSPC[24]. In this article, we discuss the current standard of treatment for mHSPC, docetaxel, ARPI, and triplet therapy and present some future considerations for this emerging field.

Docetaxel for mHSPC

The efficacy of docetaxel, an antimitotic chemotherapy agent, in the treatment of advanced PC was demonstrated in two landmark phase 3 trials in patients with mCRPC (i.e. TAX327 and SWOG 99-16)[6,25]. Both trials enrolled patients with castration-resistant disease, and docetaxel plus prednisone therapy resulted in a median OS that was approximately 2.5 months longer compared with mitoxantrone and prednisone. Since 2005, docetaxel has become the standard of care (SOC) and first-line therapy for patients with mCRPC. Since improved survival has been observed in men with mCRPC treated with docetaxel, there has been a desire to investigate the use of chemotherapy at earlier stages of the disease, i.e., in a hormone-sensitive setting.

Almost a decade after publishing of results of TAX327 and SWOG trials, the results of first phase

Table 1. Stratification of patients with mHSPC according volume and risk.

	Volume ("CHAARTED" criteria)	**Risk** ("LATITUDE" criteria)
High	≥4 bone metastasis including ≥1 outside vertebral column or pelvis and/or visceral metastasis	≥2 high-risk features of: ≥3 bone metastasis, visceral metastasis, ≥ISUP grade 4
Low	Not high	Not high

Table 2. U.S. Food and Drug Administration–Approved Agents for the Treatment of mHSPC

Treatment	Trial, Publication Year	Population	Comparator	Phase; Study Size	Outcome	Treatment vs. Control
Abiraterone acetate with prednisone	LATITUDE, 2017	mHSPC	ADT + placebo	III; 1,199	OS	53.3 vs. 36.5 mos, (HR: 0.66; 95% CI: 0.56-0.78; p<0.0001)
Abiraterone acetate with prednisone	STAMPEDE, 2017	mHSPC and locally advanced PCa	ADT alone	III; 1,917	OS	Estimated 83% vs. 73% alive at 3 yrs (HR: 0.63; 95% CI: 0.52-0.76; p<0.001)
Enzalutamide	ENZAMET, 2019	mHSPC	ADT+ nonsteroidal ART	III; 1,125	OS	Estimated 80% vs. 72% alive at 3 yrs (HR: 0.67; 95% CI: 0.52-0.86; p=0.002)
Enzalutamide	ARCHES, 2019	mHSPC – stratified by CHAARTED criteria	ADT + placebo	III; 1,150	rPFS or death	NR vs. 19 mos (HR: 0.39; 95% CI: 0.3-0.5; p<0.001)
Apalutamide	TITAN, 2019	mHSPC	ADT + placebo	III; 1,052	rPFS or death	68.2% vs. 47.5% at 24 mos (HR: 0.48; 95% CI: 0.39-0.60; p<0.001)
Apalutamide					OS	82.4% vs.73.5% alive at 24 mos (HR: 0.67; 95% CI: 0.51-0.89; p=0.005)
Docetaxel	CHAARTED, 2015	mHSPC	ADT alone	III; 790	OS	57.6 vs. 44 mos (HR: 0.61; 95% CI: 0.47-0.80; p<0.001)
Docetaxel	GETUG-AFU 15, 2013	mHSPC	ADT alone	III; 192	OS	58.9 vs. 54.2 mos (NS)
Docetaxel	STAMPEDE, 2017	mHSPC and locally advanced PCa	ADT alone	III; 1,086	OS	5-yr survival of 49% vs. 37%, (HR: 0.81; 95% CI: 0.69-0.95; p=0.009)

3 trial with docetaxel in treatment of patients with mHSPC have been published by a group of French authors[26]. The GETUG-AFU 15 trial was the first randomized phase III trial to report the use of early docetaxel in addition to ADT. Three hundred eighty-five men with mHSPC were randomly selected to receive treatment with standard ADT versus ADT plus a maximum of nine cycles of docetaxel, without concomitant prednisone/prednisolone[26]. After a median follow-up of 50 months, the trial was negative for the primary endpoint of OS, with median OS being 54.2 months in the ADT cohort and 58.9 months in the ADT/docetaxel cohort (hazard ratio [HR], 1.01; 95% CI, 0.75-1.36). Updated survival was presented in abstract form in 2015, with a median follow-up of 82.9 months[27]. There was a nonsignificant trend toward docetaxel benefit (median OS, 46.5 vs. 60.9 months; HR: 0.9; 95% CI: 0.7-1.2). When examined retrospectively, the benefit of docetaxel seemed greater in the high-volume (HV) patient subset (48% of the overall trial population) but again failed to achieve statistical significance. Several possible reasons exist for the absence of a difference in OS between the two arms in the GETUG-AFU 15 trial. First, the patient population in this trial predominantly had a low burden of metastatic disease, where the benefit of docetaxel seems to be smaller. Second, the trial was underpowered for OS as primary endpoint. Third, crossover to docetaxel at the time of progression might have improved outcomes in the control arm[26].

The larger CHAARTED trial (ECOG-ACRIN E3805), which included 790 patients, subsequently emerged with notable results first presented in 2014[17]. The addition of docetaxel to ADT for mHSPC led to a significant improvement in median OS for the entire population in this trial: 57.6 months compared with 44.0 months (HR: 0.61, 95% CI: 0.47-0.80; p<0.001). The trial was prospectively stratified by volume of disease (**Table 1**). The benefit of docetaxel seemed more pronounced in the HV subgroup than in the overall

population: median OS for HV disease improved from 32.2 months to 49.2 months (HR: 0.60, 95% CI: 0.45-0.81; p<0.001). The long-term follow-up of the CHAARTED trial after a median follow-up of 53.7 months, for the entire population, shows that those who received docetaxel plus ADT still continued to benefit compared with those who received ADT alone, with a 10-month absolute survival benefit (HR 0.73)[27]. In the low-volume (LV) population, the indolent patients weaken long-term OS with docetaxel, and only a few of the LV disease cases have aggressive disease and benefit from early docetaxel. Currently, it is not possible to identify them, and they do not constitute a considerable share affecting the survival of the entire group. In contrast, the patients with HV disease benefited even more from docetaxel after long-term follow-up (51.2 vs 34.4 months; HR: 0.63, 95% CI: 0.50-0.79; p<0.001)[28].

Since October, 2005, the STAMPEDE randomized controlled trial has recruited men with metastatic (M1), high-risk localized (N0), or node-positive (N+) prostate cancer who were newly diagnosed or had high-risk recurrent disease following previous local therapy. All were commencing first-line long-term ADT. STAMPEDE uses a multi-arm, multistage platform design to test whether the addition of different treatments, including docetaxel, zoledronic acid, celecoxib, AA, ENZ, and (among newly diagnosed M1 patients only) radiotherapy, at the time of long-term ADT initiation improves OS[19,29]. The first report for control arm A of the STAMPEDE trial, i.e. the cohort of patients with metastatic, newly diagnosed PC, treated only with ADT (n=917), revealed median failure-free survival (FFS) to be only 11.2 months, whereas median OS was 42.1 months, which was disappointing[29].

In arm C, the STAMPEDE trial, with 592 *de novo* M1 patients included, compared six cycles of docetaxel with ADT with standard ADT. At a median follow-up of 43 months, it demonstrated an OS benefit of 10 months, i.e. 81 vs 71 months (HR: 0.78; 95% CI: 0.66-0.93; p=0.006) in the ADT plus docetaxel and prednisolone arm over ADT alone[17]. Interestingly, a retrospective re-stratification for 830 patients in the STAMPEDE trial at longer follow-up showed a benefit for both high (HR: 0.81; 95% CI: 0.64-1.02) and low volume (HR: 0.76; 95% CI: 0.54-1.07) disease. The authors concluded that upfront docetaxel should be considered for patients with mHSPC regardless of their metastatic burden[30].

In addition to treatment efficacy associated with life-long treatment intensification in the mHSPC population, patient quality of life (QoL) emerges as an equally important endpoint. When assessing QoL of these patients over time and comparing Functional Assessment of Cancer Therapy-Prostate (FACT-P) scores by disease burden – for those that received only ADT, patients with LV disease had no change in the QoL over 12 months. Interestingly, in patients with HV disease, QoL declined as the disease progressed. In contrast, for patients who received both ADT and docetaxel, there was a decline in QoL those with LV disease, but there was no decline in QoL for patients with HV disease[31].

Following these trials, docetaxel with ADT became SOC in *de novo*, aggressive, high-volume, and/or symptomatic disease, or in younger, fit patients with few comorbidities aiming for shorter course treatment intensification. Fatigue, fluid retention, and stomatitis can occur in about half of patients. Febrile neutropenia, myelosuppression, and peripheral neuropathy can occur in ≥10% of patients[17,27,30].

Androgen receptor pathway inhibitors (ARPI) for mHSPC

Abiraterone acetate plus prednisone/prednisolone (AAP)

After AA, an inhibitor of androgen biosynthesis, showed OS benefit in the treatment of mCRPC in pre- and post-chemotherapy settings, its efficacy in the treatment of patients with mHSPC was demonstrated in two separate phase 3 trials, LATITUDE and STAMPEDE[10,13,18,20].

The LATITUDE trial included 1199 patients with *de novo* and high-risk (see definition in **Table 1**) mHSPC who were randomly assigned (1:1) to receive AA plus prednisone (AAP) until disease progression and ADT (AAP arm) or matching placebo plus ADT (placebo arm). The final analysis was performed after a median follow-up of 51.8 months. OS was significantly longer in the AAP arm than in the placebo arm (median 53.3 vs. 36.5 months; HR: 0.66; 95% CI: 0.56-0.78; p<0.0001)[18]. Using CHAARTED criteria in the stratification of LATITUDE trial patients examined retrospectively, the study showed that patients with HV disease benefit from AAP (HR 0.62; 95% CI 0.52-0.74, P<0.0001), while there appears to be no statistically significant benefit for LV (not reached [NR] vs. NR; HR: 0.72; 95% CI: 0.47-1.10, p=0.1242)[18,32].

The same treatment regimen was investigated in arm G of the STAMPEDE trial[20]. Over a median follow-up time of 40 months, AAP and ADT conferred an OS improvement when compared with ADT and placebo (HR: 0.63, 95% CI: 0.52-0.76)[20,31]. Using CHAARTED criteria retrospectively, there was also a clear benefit of AAP in HV disease (OS difference of 19.7%, HR: 0.54, 95% CI: 0.41-0.70, p<0.001) and for LV disease (OS difference of 4.4%, HR: 0.66, 95% CI: 0.44-0.98, p=0.041)[20,33].

In addition to OS, AAP plus ADT improved OS time to pain progression, time to PSA progression, time to symptomatic skeletal event, time to chemotherapy, and time to subsequent prostate cancer therapy as compared with ADT alone in both trials[18,20].

Both trials showed that earlier intervention with a hormonally based approach led to a deeper initial response, a longer time to the development of castration resistance and disease progression, and ultimately led to improved survival.

In mHSPC, AA is given with prednisone 5 mg daily. Standard dosing for AA is 1000 mg daily fasting because early studies found a variable effect of food on bioavailability. However, non-inferiority between 250 mg daily after a low-fat breakfast and 1000 mg fasting was found with PSA response and androgen biosynthesis in a prospective phase II study in patients with mCRPC[34]. For patients for whom cost is a factor, 250 mg with a low-fat meal can be considered.

Hypertension, hypokalemia, edema, fatigue, and hot flashes occur in at least 10% of patients. Severe hepatotoxicity occurs in about 6% of patients, and regular transaminase monitoring with dose interruption when indicated is necessary for safe administration. About 1% of patients suffered severe cardiac failure, leading to several treatment discontinuations and deaths[18,20].

Although several articles have attempted to evaluate the benefit of adding AAP to standard ADT over docetaxel added to ADT in patients with mHSPC, to date there has been no randomized clinical trial directly comparing the two drugs. Nevertheless, a direct, randomized comparative analysis of the two treatment standards for mHSPC from the STAMPEDE trial showed similar OS benefit and PC-specific survival, but AAP plus ADT was found to maintain a better QoL. The worst degree of toxicity throughout the trial period was similar but exhibited different toxicities according to well-known drug properties[35].

Enzalutamide (ENZ)

ENZ, a second generation non-steroidal AR inhibitor, like AA, has shown OS benefit in the treatment of mCRPC in pre- and post-chemotherapy settings[11,14]. Its efficacy in treatment of mHSPC was demonstrated in two key phase 3 trials, i.e. ENZAMET and ARCHES[22,23].

The ENZAMET trial randomized 1125 patients between ENZ or a first-generation nonsteroidal anti-androgen with or without early concomitant docetaxel use as well as ongoing ADT, with OS as the primary end point. Patients were stratified by disease volume according to CHAARTED criteria, planned early docetaxel therapy, planned resorptive therapy, comorbidity scores, and study site. At median follow-up time of 34 months, OS were 80% in the ENZ arm compared with 72% in the standard-care arm, with 33% reduction in death in the experimental arm (HR: 0.67; 95% CI: 0.52-0.86, p=0.002). Adding ENZ to ADT improved clinical and PSA PFS (HR: 0.40; 95% CI: 0.33-0.49, p<0.001 and HR: 0.39; 95% CI: 0.33-0.47, p<0.001, respectively)[22].

The ARCHES trial investigated the role of ENZ or placebo plus ADT in 1150 randomized patients, stratified by disease volume and previous docetaxel use, with radiological progression-free survival (rPFS) as the primary end point. At the time of the primary analysis, at 14.4 months, the risk of radiographic progression or death was significantly reduced in the ENZ arm (HR: 0.39; 95% CI: 0.30-0.50; p<0.001). Similar significant improvements in rPFS were reported in prespecified subgroups on the basis of disease volume (HV, HR: 0.44; 95% CI: 0.33-0.57; LV, HR: 0.24, 95% CI: 0.13-0.45) and prior docetaxel therapy (no prior, HR: 0.36, 95% CI: 0.27-0.48; prior, HR: 0.53, 95% CI: 0.31-0.92)[23]. The final analysis of ARCHES, after median follow-up of 44.6 months, demonstrated that ENZ plus ADT had a long-term survival benefit versus placebo plus ADT in men with mHSPC (HR: 0.66; 95% CI: 0.53-0.81; p<0.0001). This benefit was maintained irrespective of disease volume, prior local therapy, functional status, Gleason score (GS), disease localization (bone only, bone and soft tissue), and PSA[36].

Further follow-up and analysis are needed to address the OS benefit of ENZ in the subgroups of men with mHSPC treated with ADT plus docetaxel.

Fatigue, hypertension, and falls are among the significant adverse events (AEs) occurring in at least 10%

of patients. Seizures occurred in about 2% of patients with predisposing factors and in 0.4% of patients without such factors. ENZ should not be offered to patients who have seizures or who are at risk of seizures[22,23].

Apalutamide (APA)

APA is another second-generation oral non-steroidal antiandrogen. Similar to ENZ, it binds directly to the ligand-binding domain of the AR, thereby preventing AR translocation, DNA binding, and AR-mediated transcription[21]. The benefit of APA over placebo was first demonstrated in the non-metastatic CRPC setting in the SPARTAN phase III trial[37]. Its efficacy in the treatment of mHSPC was explored in the TITAN phase III trial which enrolled 1052 patients[21]. This trial had very broad eligibility criteria, and both *de novo* metastatic patients and patients with previous local therapies combined with ADT were allowed to participate in the trial. In this study, with primary end points being rPFS and OS, patients received APA or placebo alongside life-long ADT. At primary analysis, after a median follow-up time of 22.7 months, risk of radiographic progression or death was significant reduced in the APA arm (HR: 0.48; 95% CI: 0.39-0.60). OS was also longer in the APA arm (HR: 0.67; 95% CI: 0.51 to 0.89)[21]. The final analysis, after a median follow-up of 44 months, confirmed that APA plus ADT consistently improved OS, with a reduced risk of death by 35% (HR: 0.65; 95% CI: 0.53-0.79) compared with placebo plus ADT[38]. The benefit was consistent across all subgroup analyses irrespective of disease volume or risk, time of onset of metastases, functional status, GS, previous docetaxel use, and disease localization (bone only, visceral disease)[38]. After adjustment for almost 40% of placebo patients who crossed over to receive APA, the risk of death was reduced by 48% (HR: 0.52; 95% CI: 0.542-0.64)[38]. Overall, APA was well-tolerated and health-related QoL was maintained. Hot flashes, rash, and fatigue occurred in more than 20% of patients, fractures occurred in around 10%, and hypothyroidism in <10%[21].

"Triplet-therapy" for mHSPC

There are five studies that have investigated triplet-therapy in mHSPC: TITAN, ENZAMET, ARCHES, PEACE-1, and ARASENS[21-24,39,40]. Significant differences between these studies that need to be consider include the design of these trials, the inclusion of different populations, endpoints, sequential or concurrent use of docetaxel, and duration of follow-up.

In the TITAN trial, only 11% of patients included received docetaxel, which was a stratification factor in the trial. Docetaxel was administered prior to the start of APA with a median of six cycles. Among patients with prior docetaxel use, rPFS was prolonged (HR: 0.47, 95% CI: 0.22-1.01), but with a smaller benefit of APA on OS (HR: 1.27, 95% CI: 0.52-3.09). Specific safety information was not reported for the docetaxel cohort of patients[21,38].

ENZAMET was an academic, open-label trial, with 1125 randomized male participants, of whom 45% received concurrent docetaxel. Among patients receiving docetaxel, 76% of those randomized to the ENZ arm received six cycles of docetaxel compared with 65% of patients in the control arm. Although PSA PFS and clinical PFS were significantly improved by adding ENZ in patients already receiving docetaxel (HR: 0.46; 95% CI: 0.36-0.60 and HR: 0.48; 95% CI: 0.37-0.62, respectively), based on the interim analysis there was no OS benefit with triple-therapy (HR: 0.90, 95% CI: 0.62-1.31). There were reports of an increase in some toxicities with the addition of docetaxel to ENZ. However, long-term health-related QoL was maintained[22].

Among 1150 patients included in the ARCHES trial, nearly 18% received docetaxel, which was also used as a stratification factor and completed prior to start of ENZ. Of these, 90% received the full six cycles of therapy. Among patients who received docetaxel, ENZ significantly improved PFS (HR: 0.52, 95% CI: 0.30-0.89), but there was no OS benefit with the addition of ENZ (HR: 0.74, 95% CI: 0.46-1.20). There was no specific safety information for the docetaxel cohort[23,36].

PEACE-1 is a 2x2 factorial designed trial, which included 1052 men with *de novo* mHSPC, randomized to four arms in 1:1:1:1 ratio to receive standard of care (SOC), SOC + AAP, SOC + radiotherapy, or SOC + AAP + radiotherapy[24]. Docetaxel was permitted as part of SOC in 2015 and has been mandatory since 2017. Sixty percent of men received concurrent docetaxel, which was included as a stratification factor. Although the PEACE-1 trial demonstrated a significant improvement in rPFS in men with HV and LV disease (HR: 0.47; 95% CI: 0.36-0.60, p<0.0001 and HR: 0.58; 95% CI: 0.39-0.87, p=0.006, respectively),

the OS benefit was only evident in the HV group (HR: 0.72; 95% CI: 0.55-0.95, p=0.019). It is important to note that the OS data in the LV group was immature. The outcomes were significant despite the fact that a high proportion of patients in the SOC control arm crossed over to receive AAP during the course of the trial. The benefit of triplet-therapy with AAP was present regardless of local radiotherapy. There were no significant safety signals with the addition of AAP to ADT plus docetaxel[24].

The ARASENS trial was an international, randomized, double-blind, placebo-controlled phase 3 trial with approximately 1300 men with *de novo* mHSPC included and randomized in a 1:1 ratio to darolutamide (DAR) or matching placebo. All patients received standard ADT plus 6 concurrent cycles of docetaxel. Patients were stratified by disease extent and alkaline phosphatase level. The primary end point was OS[39]. After a median follow-up of 43.7 months, OS was significantly improved among patients who received DAR compared with patients who received placebo (HR: 0.68, 95% CI: 0.57-0.80, p<0.001). Adding DAR to ADT and docetaxel reduced risk of death by 32%. Median OS in the DAR arm was not reached, vs. 48.9 months in the placebo arm. The OS benefit for DAR was consistent across most prespecified subgroups (e.g. metastatic stage at initial diagnosis). DAR also significantly improved key secondary endpoints, including time to CRPC or time to pain progression. The incidence, severity, and nature of AEs were consistent with the established safety profiles of ADT and docetaxel, and rates of AEs were similar between study arms[39].

Very recently, the same group of investigators published an additional trial analysis on the benefit of DAR when assessed by disease volume and risk according to the volume and risk stratification used in the CHAARTED and LATITUDE trials (**Table 1**). This was a post-hoc trial analysis, as when ARASENS was designed, the final analysis of both the CHAARTED and LATITUDE trials had not been reported. Thus, subgroups on the basis of volume and risk categorizations were not prespecified in ARASENS. Among the total of 1305 patients, 1005 (77%) had HV disease, and a total of 912 patients (70%) had high-risk disease. Among patients with HV disease, median OS was not estimable (95% CI: 50.3 months to not estimable) in the DAR arm vs 42.4 months (95% CI: 39.7-46.0 months) in the control arm (HR: 0.69, 95% CI: 0.57-0.82). In the LV subgroup, median OS was not estimable (95% CI: not estimable to not estimable) in the DAR arm vs. not estimable (95% CI: not estimable to not estimable) in the control arm (HR: 0.68, 95% CI: 0.41-1.13). Among patients with high-risk disease, median OS was not estimable (95% CI: not estimable to not estimable) in the DAR arm vs. 43.2 months (95% CI: 40.0-48.9 months) in the control arm (HR: 0.71, 95% CI: 0.58–0.86). In the low-risk subgroup, median OS was not estimable (95% CI: not estimable to not estimable) in the DAR arm vs. not estimable (95% CI: not estimable to not estimable) in the control arm (HR: 0.62, 95% CI: 0.42-0.90). Taken together, HV/LV and high-risk/low-risk mHSPC, treatment intensification with DAR, ADT, and docetaxel increased OS in all four post-hoc defined patient subgroups[40]. The authors concluded that this triplet-therapy should be new the SOC for patients with mHSPC.

Future considerations

The clinical heterogeneity of PC highlights the challenges in treating of patients with mHSPC. However, we can rightly ask ourselves whether knowledge of time of onset of metastatic disease (e.g. *de novo* vs. metachronous) and its volume (e.g. HV vs. LV) is sufficient in choosing the optimal therapy for our patients and whether the mHSPC treatment approach needs to be further intensified in the form of triplet-therapy or by adding different targeted agents.

In addition to existing clinical biomarkers, we are still looking for true molecular predictive biomarkers in mHSPC, since we understand very little about patient and tumor heterogeneity as it impacts cancer in men with mHSPC. PSA kinetics may be useful prognostic markers for men on ADT, with longer survival associated with more sustained and complete PSA response. Circulating biomarkers are an important area of research. An interesting example is a correlative study from the CHAARTED trial, showing an association between the luminal B subtype and both poorer OS with ADT alone and benefit from the addition of docetaxel [41].

Nevertheless, in the past few years, several analyzes have demonstrated the importance of certain gene alterations in disease progression but also in response to available therapy in mCRPC. A multi-institutional integrative clinical sequencing analysis revealed that the majority of affected individuals with

mCRPC harbor clinically actionable molecular alterations[42]. Of particular importance in the progression of mCRPC are alterations of AR (i.e. amplification and mutations), p53 (i.e. mutations), PTEN deficiency (i.e. mutations and homologous deletion) with activation of the PI3K/AKT signaling pathway, RB1 (i.e. mutations and homologous deletion), and DNA repair genes, i.e. BRCA 1 and BRCA 2 (i.e. mutations and loss of heterogeneity). A study published in 2019 outlines these findings. Using comprehensive genomic profiling (CGP) to analyze thousands of tumor samples from men with advanced PC, the researchers identified that 57 percent of the samples evaluated had genomic characteristics that suggested the tumors were candidates for targeted therapies[43]. These findings have resulted in the introduction of new therapies in progressive mCRPC such as PARP inhibitors (PARPi) or PI3K/AKT pathway inhibitors (e.g. ipatasertib)[44-47]. These genomic alterations are the cause of progression in mCRPC but are also found in mHSPC, which consequently led to several clinical trials examining intensified targeting of the AR axis plus inhibition of the PI3K/AKT pathway with capivasertib (CAPItello-281 trial) or plus DNA damage repair inhibition with PARPi (TALAPRO-3 and AMPLITUDE trials with talazoparib and niraparib, respectively)[48-50]. Furthermore, several trials are underway with a focus on checkpoint inhibition and immune modulation in mHSPC. Most promising is the ongoing MK3475-991 trial that investigates the efficacy and safety of pembrolizumab plus ENZ plus ADT versus placebo plus ENZ plus ADT. Primary endpoints are rPFS and OS[51]. In contrast to many other tumor sites, the benefit of immune check point inhibitors is yet to be proven in PC. Based on data published so far, the response of an unselected population of patients with PC on immunotherapy is limited.

Discussion

Several important points need to be emphasized. First, are there still patients with mHSPC where ADT monotherapy is still appropriate, and can we predict patients where treatment intensification will do more harm than good? In this context, it is reasonable to examine some real-world data on the uptake of intensified therapy in patients with mHSPC. A retrospective analysis of the Medicare database from 2009-2018, with more than 35000 men with mHSPC revealed that less than one-third of patients received treatment intensification by 2018, possibly due to patient or disease characteristics, provider awareness or therapeutic inertia, or cost[52]. The report from the Canadian province of Ontario showed that of 3500 patients with *de novo* mHSPC commencing testosterone suppression in the 5 years after the CHAARTED data were presented, 78.6% were offered no additional treatment. Only about 11% received docetaxel, and 1.5% received AAP. The survival of patients in this study was found to be lower than in the relevant clinical trials[53]. Regarding access to ARPI in mHSPC, so far there is no published real-world data; however, projected estimates suggest similar uptake in only a minority of patients with mHSPC. In the era of therapeutic options that have been demonstrated to be more effective than ADT monotherapy, such an approach should not be acceptable in men with mHSPC. Additionally, there is a relative paucity of data on predictive biomarkers of response or toxicity to docetaxel or ARPI in the mHSPC setting. There is no consensus definition of docetaxel eligibility, though many patients are "rightfully" excluded from chemotherapy. However, very few patients should be totally excluded from ARPI. Nevertheless, there is likely a subgroup of patients with mHSPC who will not benefit from intensified therapy; at present, we lack the tools to identify who they are. Consequently, the optimal treatment strategy should not be based only on the results of relevant clinical trials, volume of disease, or time of onset of metastasis, but also on relevant clinical data such as the patients' life expectancy, comorbidities, concomitant medications, or preferences.

Apparently, with the arrival of the results of relevant trials in mHSPC, debates on optimal treatment of men with mHSPC, according to the volume of disease or time of onset of metastasis, are coming to an end. With the approval of APA and ENZ in the mHSPC setting, the decision on which patients should receive chemotherapy and which should receive ARPI becomes much simpler. There are strong data that in men with mHSPC the addition of ARPI to ADT prolongs survival and delays the development of castration resistance, regardless of volume, risk, or time of onset of metastasis. After the famous entry into this segment in 2015, docetaxel chemotherapy is moving towards later stages of the disease, i.e. castration-resistant disease. The exception are patients with a very high-risk disease (e.g. *de novo* high-volume disease with visceral metastases with adequate organ func-

tion) where chemotherapy, but never as monotherapy, still has its place. Continuous hormonal treatment of mHSPC has trumped chemotherapy. Even in the aforementioned specific cases where docetaxel chemotherapy is indicated, ARPI must be continued until progression. However, the dilemma about the best combination of triplet therapy still remains. So far, the strongest evidence for triplet therapy was provided by the PEACE-1 and the ARASENS trials, with a combination of ADT, docetaxel, and AAP in high-volume patients and ADT, docetaxel, and DAR in almost all subgroups of patients with mHSPC, respectively. The level of evidence for triplet therapy with APA or ENZ is lower, as shown in the TITAN, ENZAMET, and ARCHES trials.

Conclusion

The introduction of docetaxel and ARPI in mHSPC has changed the landscape of treatment for advanced PC. Data from trials with docetaxel and ARPI suggest that monotherapy with ADT is no longer acceptable for treatment of men with mHSPC. Systemic treatment options in this setting include doublets consisting of ADT plus AAP, APA, or ENZ, or ADT plus docetaxel; and a triplet combination of ADT plus docetaxel and AAP or DAR, especially for patients with *de novo* high-risk or high-volume disease. More data are needed regarding the potential combination of ADT plus docetaxel and either APA or ENZ. Finally, further elucidation of the biology of different groups of mHSPC to identify correlates of different clinical behavior may be helpful. The transcriptomic biomarker analysis of patient samples from major practice changing trials in mHSPC could optimize patient selection for different treatment strategies and help providers in decision-making in everyday practice.

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Sažetak

NOVA PARADIGMA U SISTEMSKOM LIJEČENJU UZNAPREDOVALOG RAKA PROSTATE: ŠTO RANIJE TO BOLJE ILI ŠTO VIŠE TO BOLJE

T. Omrčen i *J. Murgić*

Terapija deprivacijom androgena (ADT) već desetljećima je osnova liječenja uznapredovalog raka prostate (APC). Uvođenje docetaksela i inhibitora signalnog puta androgenog receptora (ARPI; abirateron, enzalutamid, apalutamid) u liječenju metastatskog hormonski osjetljivog PC (mHSPC) promijenilo je terapijski pristup APC-u. Podaci iz studija s docetakselom (CHAARTED, STAMPEDE) i NHT (STAMPEDE, LATITUDE, ENZAMET, ARCHES, TITAN) ukazuju da monoterapija ADT-om više nije prihvatljiva za liječenje muškaraca s mHSPC-om. Sustavne mogućnosti liječenja u ovom slučaju uključuju: kombiniranu terapiju koja se sastoji od ADT-a i abiraterona (AAP) ili apalutamida (APA), ili enzalutamida (ENZ); ADT u kombinaciji s docetakselom ostaje opcija u slučajevima gdje ARPI nije dostupan ili kombinacija ADT-a, docetaksela s ARPI nije moguća, i trostruka terapija koja se sastoji od kombinacije ADT-a, docetaksela i AAP-a ili darolutamida (PEACE-1, ARASENS studije), posebno za pacijente s visokim rizikom/visokim volumenom sinkrone bolesti. Potrebni su daljnji podaci o potencijalnoj kombinaciji ADT-a s docetakselom i APA-om ili ENZ-om. Prilikom odluke o liječenju pacijenta s mHSPC-om, uz rezultate relevantnih studija, treba uzeti u obzir opće stanje pacijenta, njegove komorbiditete i ostale lijekove, afinitete, dostupnost i toksičnost lijekova, te troškove liječenja. Naposljetku, daljnje razjašnjenje biologije različitih skupina mHSPC-a kako bi se identificiralo različito kliničko ponašanje moglo bi pomoći u odabiru optimalnog liječenja tih pacijenata. Analiza transkriptomskih biomarkera uzoraka pacijenata iz velikih, studija koje mijenjaju praksu u mHSPC-u mogla bi optimizirati selekciju pacijenata za različite terapijske strategije i pomoći liječnicima u donošenju odluka u svakodnevnoj praksi.

Ključne riječi: *hormonski osjetljivi rak prostate, docetaksel, inhibitori signalnog puta androgenog receptora, dvojna terapija, trojna terapija*