Acta Clin Croat (Suppl. 3) 2022; 61:81-85
doi: 10.20471/acc.2022.61.s3.12

Professional Paper

SYSTEMIC TRIPLE THERAPY IN METASTATIC HORMONE SENSITIVE PROSTATE CANCER (MHSPC)

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SUMMARY: For many years, androgen deprivation therapy (ADT) as monotherapy has been the gold standard for metastatic hormone-sensitive prostate cancer (mHSPC) treatment. Several studies have been published within the last decade demonstrating a significant survival advantage resulting from combining the treatment with standard ADT plus docetaxel or androgen receptor targeted therapy (ARTA) compared to ADT monotherapy. Recently published data of the PEACE-1 and ARASENS trials suggest that in the future, triple therapy might be a treatment option for patients with mHSPC.

Key words: *hormone-sensitive prostate cancer; systemic therapy; novel hormonal therapy; taxanes; triple therapy*

Introduction

Androgen-deprivation therapy (ADT) with luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists or surgical castration (orchiectomy) has been the backbone of treatment of advanced prostate cancer (PC) for many decades [1]. Since the mid-1980s, it has been attempted to improve the outcome for the patients with advanced disease using intermittent ADT or the addition of first-generation antiandrogens (flutamide, bicalutamide) [2,3]. However, despite all attempts to improve the efficiency of ADT for the patients with metastatic PC, median duration of sensitivity to ADT is usually 2-3 years, and the resistance to ADT occurs in most patients. Major advances in understanding the role of androgen receptor (AR) signalling pathway and AR-independent pathways in biology and progression of PC led to the development of new agents at the beginning of the 21st century [4-6]. After showing their antitumoral effects in castration-resistant disease, the effect of these compounds has been investigated in combination with standard ADT in mHSPC patients [7]. The spectrum of patients starting ADT for mHSPC is quite vast, and the pattern of disease is now known to be very important. There are patients who present with de novo metastatic disease, and others with metachronous disease who present after previous radical prostatectomy or radiotherapy with curative intent [8,9]. Some have a minimal disease (low volume, LV), and some have widespread disease (high volume, HV) seen on conventional imaging modalities that have led to stratification in several categories according to recent mHSPC trials [10,11] (see Table

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1). So far, four novel compounds have been tested for intensified combined (double) therapy in mHSPC: docetaxel (the taxane), abiraterone, enzalutamide and apalutamide (ARTA) (see Table 2).

Table 1. Stratification of mHSPC.

Stratification	Criteria
High volume vs low volume (CHAARTED)[10]	High volume disease includes at least 1 of the following: • ≥4 bone lesions with ≥1 beyond the vertebral bodies/ pelvis • Visceral metastasis
High risk vs low risk (LATITUDE)[11]	High risk disease includes at least 2 of the following: • ≥3 bone lesions • Visceral metastasis • Gleason score ≥8

Table 2. Combination therapy studies in mHSPC.

Trial	Intervention	Prior local therapy (%)	Docetaxel use (%)	Median follow up (months)	Overall Survival Benefit (HR; 95% CI)
CHAARTED[10]	ADT plus docetaxel 75 mg/m2 every 3 weeks for 6 cycles vs. ADT	37	/	54	0.72; 0.59–0.89
STAMPEDE C (M1 subgroup)[7]	ADT plus docetaxel 75 mg/m2 every 3 weeks for 6 cycles vs. ADT	/	/	43	0.76; 0.62–0.92
LATITUDE[11]	ADT plus abiraterone 1 g/prednisone 5 mg daily vs. ADT	0	/	52	0.66; 0.56–0.78
STAMPEDE G (M1 subgroup)[7]	ADT plus abiraterone 1 g/prednisone 5 mg daily vs. ADT	6	/	34	0.61; 0.49–0.79
ARCHES[15]	ADT plus enzalutamid 160 mg daily vs. ADT	27	18	45	0.66; 0.53–0.81
ENZAMET[16]	ADT plus enzalutamid 160 mg daily vs. ADT	39	45	34	0.67; 0.52–0.86
TITAN[13]	ADT plus apalutamide 240 mg daily vs. ADT	16	11	44	0.65; 0.53–0.79

ADT = androgen deprivation therapy, CI = confidence interval, HR = hazard ratio.

Methods

The literature search was made in Pubmed records with the keywords: metastatic hormone sensitive prostate cancer, novel hormonal therapy. All clinical trials and review articles written in English were looked through. Conference abstracts were also included, and cross-matching references were used to find additional articles.

Discussion

Five trials have investigated the potential of more intensified triple therapy in mHSPC: TITAN, ARCHES, ENZAMET, PEACE-1 and ARASENS (see Table 3). The factors that are important to consider when comparing the results obtained in such trials include different patient populations, endpoints, and the question whether docetaxel has been given sequentially or concurrently, and the duration of follow-up.

Among 1,052 men with mHSPC included in the TITAN trial, 63% had high-risk disease and 81% had synchronous mHSPC. Only 11% received docetaxel, which was a stratification factor in the trial. Docetaxel was completed before starting with apalutamide, and was delivered with a median of six cycles. Among the patients with prior docetaxel use, although rPFS was prolonged (HR 0.47, 95% CI 0.22–1.01), there was no benefit in receiving the apalutamide for OS (HR 1.12, 95% CI, 0.59-2.12). There was no specific information reported on the safety for the docetaxel cohort of patients [12,13].

In the ARCHES trial, among 1,150 included men, 63% had high-risk disease and 67% were with synchronous mHSPC. Almost 18% of patients received docetaxel, which was also used as a stratification factor and completed before starting the treatment with enzalutamide. 90% of these patients received full six cycles of therapy. Among the patients who received docetaxel, enzalutamide significantly improved PFS (HR 0.52, 95% CI 0.30-0.89), but there was no OS benefit in adding enzalutamide (HR 0.74, 95% CI 0.46-1.20). There was no specific information reported on the safety for the docetaxel cohort [14,15].

In the open-label ENZAMET trial, 53% out of 1,125 randomized men had HV disease and 45% received concurrent docetaxel. Among those receiving docetaxel, 76% of patients randomly assigned to the enzalutamide arm received six cycles of docetaxel compared to 65% of patients in the control arm. Based on the interim analysis, there was no OS benefit resulting from the triplet therapy (HR 0.90, 95% CI 0.62-1.31), but PSA PFS and clinical PFS were significantly im-

Table 3. Triple therapy with ADT + docetaxel as standard of care in mHSPC.

Trial	Patients Receiving Triple Therapy (n)	Start of Docetaxel Application to NHT	Docetaxel Cycles	Effect of NHT on OS HR; 95% CI
ARCHES[15]	205	Prior	Full 6 cycles administered in 86% of patients	0.74; 0.46–1.20
ENZAMET[16]	503	Prior (35%) and concomitant (65%)	Full 6 cycles administered in 71% of patients	0.90; 0.62–1.31
TITAN[13]	58	Prior	In median, 6 cycles administered	1.12; 0.59–2.12
PEACE-1[17]	710	Concomitant	Full 6 cycles administered in 100% of patients	0.75; 0.59–0.95
ARASENS[19]	651	Concomitant	Full 6 cycles administered 88% of patients	0.68; 0.57-0.80

NHT= new hormonal therapy HR = hazard ratio; CI = confidence interval; OS = overall survival.

proved by adding enzalutamide 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). There was an apparent increase in some toxicities reported when adding the docetaxel to enzalutamide. However, long-term health-related QoL was maintained [16].

The PEACE-1 is a 2x2 factorial designed trial, with 1052 de novo mHSPC men included, and randomized to four arms in 1:1:1:1 ratio to receive the standard of care (SOC), SOC + abiraterone plus prednisone (AAP), SOC + radiotherapy, or SOC + AAP + radiotherapy. Docetaxel was permitted as a part of SOC in 2015 and it has been mandatory since 2017. Given the evolving control arm in this study, 60% of men received concurrent docetaxel that was included as a stratification factor. PEACE-1 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) while the OS benefit was only evident in the HV group (HR 0.72; 95% CI 0.55-0.95, p=0.019). Notably, 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 triple-therapy with AAP was indicated in the patients receiving and not receiving local radiotherapy. There were no major safety signals related to the addition of AAP to ADT plus docetaxel [17].

One of the most promising trials to obtain more evidence for the need to further intensify the mHSPC treatment, is the ARASENS study. This international, randomized, double-blind, placebo-controlled phase 3 trial is being conducted on more than 300 sites in 23 countries. Approximately 1300 men with newly diagnosed mHSPC were randomized in a 1:1 ratio to another second-generation antiandrogen darolutamide or matching placebo. All patients received standard ADT plus 6 cycles of docetaxel. The patients were stratified by disease extent and alkaline phosphatase level. The primary end point is OS [18]. At the American Society of Clinical Oncology Genitourinary Cancer Symposium in February 2022, the first OS results were presented. After median follow up of 43.7 months, compared to the patients who received placebo, OS was significantly improved among the patients who received darolutamide (HR 0.68, 95% CI 0.57-0.80, p<0.001). After adding darolutamide to ADT and docetaxel, the risk of death was reduced by 32%. Median OS in darolutamide arm was not reached vs 48.9 months in placebo arm. Darolutamide improved OS despite the high rate of subsequent life-prolonging systemic treatment in placebo arm. The OS benefit in administering darolutamide was consistent across most prespecified subgroups (e.g. regardless of the extent of disease or metastatic stage at initial diagnosis). Darolutamide also significantly improved key secondary endpoints, including time to CRPC or time to pain progression. The incidence, severity, and the nature of adverse events (AEs) were consistent with the established safety profiles of ADT and docetaxel. The rates of AEs were similar both in the darolutamide and placebo arms. The authors concluded that darolutamide in combination with ADT and docetaxel should become a new SOC for the treatment of mHSPC [19].

Conclusion

Systematic combination therapy has dramatically changed the treatment landscape in mHSPC within the last decade. Currently, the combination therapy of ADT plus docetaxel or ARTA is the gold standard in the treatment of majority of patients with mHSPC. The patients receiving triplet therapy on TITAN and ARCHES comprised a minority of the study population and were treated in rapid sequence, demonstrating no benefit for the addition of docetaxel to ADT plus apalutamide or enzalutamide, respectively. ENZAMET showed a strong rPFS benefit for the addition of concurrent docetaxel to ADT plus enzalutamide, but no OS benefit – although only 50% of the planned events occurred at the time of this analysis, so the data is immature. The data from PEACE-1 demonstrated a significant improvement in rPFS in all men with mHSPC, but the OS benefit was evident only in the HV group. Again, OS data in the LV group was immature. The data from ARASENS trial demonstrated the OS benefit for the addition of darolutamide to ADT plus docetaxel across most prespecified subgroups. In conclusion, although the triplet therapy is intriguing, we must establish the doublet therapies first.

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Sažetak

TROJNA SUSTAVNA TERAPIJA ZA METASTATSKI HORMON-OSJETLJIVI RAK PROSTATE

T. Omrčen

Dugi niz godina, terapija deprivacije androgena (ADT) kao monoterapija bila je zlatni standard liječenja metastatskog hormonski osjetljivog raka prostate (mHSPC). U posljednjem desetljeću objavljeno je nekoliko studija koje pokazuju značajnu prednost u preživljavanju kombiniranim liječenjem ADT uz docetaksel ili terapijom koja cilja androgeni receptor (ARTA) u usporedbi s ADT u monoterapiji. Nedavno objavljeni podaci ispitivanja PEACE-1 i ARASENS sugeriraju da bi u budućnosti trostruka terapija mogla biti opcija liječenja pacijenata s mHSPC.

Ključne riječi: *hormonski osjetljiv rak prostate; sustavna terapija; nova hormonska terapija; taksani; trostruka terapija*