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WHO SHOULD RECEIVE NOVEL HORMONAL THERAPY WITH ANDROGEN DEPRIVATION THERAPY IN METASTATIC HORMONE SENSITIVE PROSTATE CANCER?

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SUMMARY – Treatment with androgen deprivation (ADT) has for many years been a standard treatment for patients with metastatic hormone-sensitive prostate cancer (mHSPC). However, several phase 3 randomized trials have completely changed the therapeutic approach for these patients. First, two phase 3 trials, CHAARTED and STAMPEDE, showed that docetaxel added to ADT improves survival of patients with mHSPC. Here we present an overview of the most important trials in this setting: STAMPEDE, LATITUDE, ARCHES, ENZAMET and TITAN in which abiraterone acetate, enzalutamide and apalutamide combined with ADT achieved significant improvement in overall survival of patients with mHSPC compared with ADT only. All three agents combined with ADT became new standard of therapy for this group of patients.

Key words: *Metastatic, Hormone Sensitive, Prostate Cancer, Novel Hormonal Therapy*

Introduction

Treatment with androgen deprivation (ADT) for many years has been, and remains, the standard form of treatment for patients with metastatic hormone-sensitive prostate cancer (mHSPC). Still, several phase 3 randomized trials have completely changed the therapeutic approach for these patients. Here we present an overview of the results of the most important trials, published in recent years, and discuss optimal treatment approach in this setting.

Methods

A review of literature by searching Pubmed with the keywords was performed: metastatic hormone-sensitive prostate cancer, novel hormonal therapy. All clinical trials and review articles written in English were reviewed. Conference abstracts were also included, and cross-matching references were used to find additional articles.

Discussion

The CHAARTED[1] and STAMPEDE[2] trials showed significant improvement in overall survival (OS) by the addition of docetaxel to ADT to a much greater extent than when used in castration-resistant prostate cancer (CRPC). The CHAARTED trial randomized 790 men with mHSPC to docetaxel plus ADT or ADT alone. After a median follow-up of 54 months, patients in the combination arm experienced longer OS then those in the ADT arm (57.6 vs 47.2 months, HR 0.72, p=0.002). A greater benefit was observed in patients with large volume disease (HVD) (HR 0.63) compared to patients with low volume disease (LVD) who did not achieve benefit in OS (HR 1.04)[1]. STAMPEDE trial included patients both with

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M0 and M1 HSPC but the extent of disease was not evaluated. Results in the M1 population confirmed survival advantage of adding docetaxel to ADT seen in the CHAARTED trial. The median OS in 1087 patients with M1 disease was 5.4 years in combination arm versus 3.6 months in ADT arm[2]. Based on these two trials, a combination of docetaxel and ADT in mHSPC patients became a standard of care in this setting.

In February 2018, abiraterone acetate (AA) was approved by the Food and Drug Administration (FDA) for treatment of patients with high-risk (HR) mHSPC, based on significant OS gain demonstrated in the LATITUDE[3] (HR 0.62, p <0.0001) and STAMPEDE[4] (HR 0.63, p <0.0001) trials. Although the combination of ADT with another agent having a different mechanism of action made sense, the thought that intensifying hormonal therapy would lead to such improvements in survival was intriguing. The LATITUDE data helped consolidate the theory that earlier intervention with a hormonally based approach leads to a more profound initial response and longer time to resistance and disease progression, with all this leading to improved survival[3].

We already had suggestions from mCRPC trials that response and survival advantages with hormonally based therapies appeared more pronounced in patients with a lower tumor burden (i.e., lower prostate-specific antigen [PSA] levels, less pain and fewer sites of metastases). This could be explained by the idea that with a lower tumor volume, there may be fewer hormone-insensitive clones that would be unresponsive to an androgen receptor signaling/targeted inhibitor. Given the results of the CHAARTED and LATITUDE trials, the general consensus was, however, to limit the use of either docetaxel or AA to patients with newly diagnosed high volume (HV) or high-risk (HR) mHSPC. Patients again questioned why we were reluctant to intensify treatment in lower-risk (LR) patients and in those whose disease progressed from a localized to metastatic state. Again, the lack of convincing data prevented us from doing things that actually made sense.

With evidence of the effectiveness of second-generation hormonal therapy in this indication, enzalutamide (ENZ), appalutamide (APA), and darolutamide (DAR) target the same patient population. Three phase 3 trials examined ENZ in this indication: ENZ in combination with ADT in ARCHES[5] and ENZAMET[6] and in combination with AA and ADT in branch J of STAMPEDE[7]. Additionally, APA in combination with ADT was examined in a phase 3 trial, TITAN[8], and a phase 3 trial, ARASENS was recently launched, which aims to examine the combination of DAR, ADT and docetaxel[9].

At the ASCO 2019 meeting for genitourinary the results of an interim analysis of the ARCHES study on 1,146 patients were presented[5]. The study included patients with low volume disease (LVD) and high-volume disease (HVD) with or without prior docetaxel treatment. After a median follow-up of 14.4 months, the combination of ENZ and ADT reduced the risk of radiological progression or death by 61% (HR 0.39, p <0.0001); the median radiological progression-free survival (rPFS) was not reached compared to 19.4 months in the ADT-only arm. It is important to emphasize that benefit was observed in all the subgroups observed, including patients who had previously received docetaxel (HR 0.53) and who had HVD (HR 0.44)[5]. In addition to delayed progression, ENZ plus ADT resulted in a significant prolongation of time to PSA progression (HR 0.19, p <0.0001), extending the time to the beginning of treatment with a new treatment line (HR 0.28, p <0.0001) and extending the median time to developing castration resistance (NR vs. 13.9 months, HR 0.28, p <0.0001). These results are very promising, especially regarding patient population included in the study: approximately 63% had HVD, 67% had a Gleason score of ≥8 and 17.8% had previously received docetaxel. At the time of the interim analysis, 93% of patients were alive, so OS data are immature. Equally important, the combination of ENZ and ADT was well tolerated with a toxicity profile consistent with mCRPC[5].

At the ASCO annual meeting in June 2019 the results of another significant ENZ study in this indication, ENZAMET, were presented[6]. This study included 1,125 patients with HVD and LVD randomized into 2 groups: an LHRH agonist or antagonist plus an ENZ or a standard non-steroidal antiandrogen. After a median follow-up of 34 months, 102 patients died in the ENZ group versus 143 died in the standard-therapy group (HR 0.67, P = 0.002). OS at 3 years was 80% in the ENZ group versus 72% in the standard-therapy group. Better results with ENZ were also reported regarding PSA PFS (HR 0.39; P <0.001)

and clinical PFS (HR 0.40; P <0.001). In this trial, the toxicity profile of ENZ was similar to that in ENZ studies in patients with mCRPC[6].

According to these reports, ENZ plus ADT is another therapeutic option for patients with mHSPC.

Unfortunately, there is no direct comparison between AA and ENZ in this indication, and the goals in different studies were different. rPFS was not a target in the STAMPEDE study[2] due to the lack of routine radiological follow-up, so, rPFS from these two ENZ trials are comparable to rPFS in LATITUDE trial[3]. According to the ARCHES study, ENZ may be more effective than AA in this indication, based on the higher multi-objective benefit achieved: rPFS (HR 0.39 in ARCHES[5] and HR 0.47 in LATITUDE[3]), time to PSA progression (HR 0.19 in ARCHES[5] and HR 0.30 in LATITUDE[3]) and time to new therapy line (HR 0.28 in ARCHES[5] and HR 0.42 in LATITUDE[3]). However, it is important to emphasize that the difference in population of patients included between the two studies may explain the difference in benefit obtained.

The TITAN trial included 1,052 HVD and LVD mHSPC patients, who were randomized to receive APA or placebo, added to ADT[8]. It was one of the first studies to specifically target the LR mHSPC patient population. Previous localized disease therapy as well as docetaxel administration (11% of subjects) were allowed. After a median follow-up of 22.7 months, the percentage of patients without radiological progression after 24 months was 68.2% in the APA arm versus 47.5% in the placebo arm (HR 0.48, P <0.001). OS after 24 months was better in the APA arm compared to the placebo arm (82.4% vs. 73.5%; HR 0.67; P= 0.005). Actually, the results were surprising in that APA was able not only to delay disease progression, but also to significantly improve OS in men with the whole spectrum of mHSPC. It was also surprising how quickly this difference in OS was demonstrated. It is important to note that patients were well managed, and sequential therapy was appropriately used. Another revealing aspect of the TITAN trial is that the survival benefit appeared to be at least as good in patients with LVD as in those with HVD, and regardless of whether a patient was newly diagnosed or had disease progression from a localized to a metastatic state. It is important to note that those with combined visceral and bone metastases do not do as well. Toxicity profile did not differ significantly between groups[8].

Conclusion

It is now clear that there are a number of very effective therapeutic options for patients with mHSPC and that with the ongoing DAR study in this indication, the decision on the optimal drug in this indication will be even more complicated. Similar to what we experienced in mCRPC, we are now going in mHSPC with four effective agents, as well as finding that treatment is relevant in LV mHSPC. The objective should now be to aim for the best response upfront.

For HV/HR mHSPC, we now have several available effective agents, and deciding which to use will include tumor/patient characteristics, cost, and our personal biases/preference as physicians. ADT alone appears to be suboptimal care nowadays. For patients who do not have HVD or HR disease, there will still be controversy regarding the upfront use of APA or ENZ in all patients vs. waiting until mCRPC to introduce subsequent therapy.

The results of all mentioned trials strongly suggest that early aggressive therapy in all patients with mHSPC is more effective than sequential treatment. With a median time to CRPC in patients with metastatic disease of only 1 year, the added burden of treatment to the patient, as well as to the health-care system, appears well worth the cost.

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Sažetak

TKO BI TREBAO PRIMITI NOVU HORMONSKU TERAPIJU S TERAPIJOM SMANJENJA ANDROGENA U METASTATSKOM HORMON OSJETLJIVOM RAKU PROSTATE?

T. Omrčen

Liječenje deprivacijom androgena (ADT) već dugi niz godina je standardni oblik liječenja bolesnika s metastatskim hormonski osjetljivim rakom prostate (mHSPC). No, nekoliko studija faze 3 potpuno je promijenilo terapijski pristup za ove bolesnike. Najprije su dvije studije faze 3, CHAARTED i STAMPEDE, pokazale da dodatak docetaksela ADT poboljšava preživljenje bolesnika s mHSPC. Ovdje predstavljamo pregled najvažnijih ispitivanja u ovoj indikaciji: STAMPEDE, LATITUDE, ARCHES, ENZAMET i TITAN u kojima su abirateron acetat, enzalutamid i apalutamid u kombinaciji s ADT-om postigli značajno poboljšanje ukupnog preživljavanja bolesnika s mHSPC-om u usporedbi samo s ADT-om. Dakle, sva tri lijeka u kombinaciji s ADT-om postali su novi standard terapije za ovu skupinu bolesnika.

Ključne riječi: *metastatski, hormonski osjetljiv, rak prostate, nova hormonska terapija*