WHICH PATIENTS WILL BENEFIT MOST FROM DOCETAXEL ADDITION TO ANDROGEN DEPRIVATION THERAPY (ADT) IN METASTATIC CASTRATE-SENSITIVE PROSTATE CANCER (mCSPC)?

Marija Gamulin¹², Marko Bebek¹² and Milena Gnjidic¹

¹Department of Oncology, University Hospital Centre Zagreb, Zagreb, Croatia; ²School of Medicine, University of Zagreb, Zagreb, Croatia

SUMMARY – Docetaxel improved the outcome of patients with mCSPC and became standard of care after CHAARTED, STAMPEDE arm C and GETUG-AFU 15 clinical trials and after subsequent meta-analysis. Patients with high-volume (CHAARTED definition) and high-risk (LATITUDE definition) disease, who have good performance status and are fit for chemotherapy, seem to benefit the most from addition of docetaxel to the androgen deprivation therapy. Results from TITAN trial with apalutamide showed the activity in the same setting. However, predictive biomarkers are still lacking. We have direct evidence of overall survival benefit from abiraterone, apalutamide and enzalutamide for patients with high-volume disease who are not fit for chemotherapy, as well as for patients with low-volume disease. Clinical trials will show is there place for triple therapy in clinical practice. Before obtaining the results of new clinical trial results, physicians should base their treatment decision on risks and benefits of each current approach and consider the patient’s other health issues such as access, costs, patient and patient’s preferences.

Key words: Hormone-sensitive, Prostate Cancer, Docetaxel, Androgen-receptor Inhibitors, High-volume, High-risk

Introduction

Although androgen-deprivation therapy (ADT) is still the backbone of treatment, addition of docetaxel, abiraterone acetate, enzalutamide or apalutamide has improved the outcome for patients with mCSPC and has become a standard of care. To date, no head-to-head comparisons between current treatment options are available¹⁵.

Evidence on docetaxel in treatment of mCSPC

ADT plus docetaxel for six cycles is considered a standard of care for high-volume mCSPC based on CHAARTED, STAMPEDE arm C and GETUG-AFU 15 clinical trials. CHAARTED and STAMPEDE arm C demonstrated that up-front docetaxel plus ADT improves overall survival (OS) of patients with mCSPC. In CHAARTED clinical trial, benefit from ADT plus docetaxel in terms of median OS was 51 months and with ADT alone it was 34 months; HR 0.63; 95% CI, 0.50–0.79. Similar to CHAARTED, ADT plus docetaxel significantly improved median OS compared with ADT alone in STAMPEDE arm C (81 months vs. 71.3 months; HR 0.78; 95% CI, 0.66–0.93). Subsequent meta-analysis established ADT plus docetaxel as a standard of care for fit patients with high-volume or high-risk mCSPC.

Predictive biomarkers are needed to select patients for optimal treatment. Until those are identified, ADT plus docetaxel may be considered for patients with high-volume disease mCSPC (presence of visceral...
metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis, according to CHAARTED definition) or high-risk disease (presence of at least two of three criteria [of a Gleason score of ≥8, at least three bone lesions and the presence of visceral metastasis], according to the LATITUDE definition), who have a good performance status, desire shorter total treatment time or have concerns about prescription drug costs.

Position of docetaxel in comparison to other, newer androgen receptor inhibitor

For patients with high-volume disease and not fit for chemotherapy as well as for patients with low-volume disease, we have direct evidence of overall survival benefit from abiraterone, apalutamide and enzalutamide added to testosterone suppression. There is a possibility that with a lower tumor volume, there may be fewer hormone-insensitive clones that would be unresponsive to an androgen receptor signaling/targeted inhibitor, so we can conclude that with high tumor volume it would be beneficial to combine chemotherapy with androgen receptor signaling/targeted inhibitor. It is undeniable that some men with high-volume disease might benefit from triple therapy with androgen-deprivation therapy, docetaxel and an androgen-receptor inhibitor, which may further delay symptomatic and radiographic disease progression or death. But, in 2019, there has been no clear overall survival benefit from docetaxel plus enzalutamide (ENZAMET, ARCHES clinical trials; HR = 0.90, 95% CI = 0.62–1.31) or apalutamide (TITAN clinical trial; HR = 1.27, 95% CI = 0.52–3.09), although these confidence intervals are wide and do not exclude a clinically meaningful survival benefit. Overall survival results of the TITAN trial were surprising, but another revealing aspect of the TITAN trial is that survival benefit appeared to be at least as good in patients with low-volume disease as in those with high-volume disease, and regardless of whether the 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. Further follow-up and meta-analyses, as well as results from the ARASENS clinical trial (darolutamide with docetaxel), can address questions about combination therapy.

Discussion

The ultimate choice for an individual patient depends on the physician detailing risks and benefits of each approach and considering patient’s other health issues such as access, costs and patient’s preference. We need to bear in mind that previous exposure to docetaxel or an ARTA has different clinical and biological implications because, as they were administered in an early disease phase, their activity is likely to be different from that observed in mCRPC patients.

Androgen-deprivation therapy alone appears to be suboptimal care in 2019 and is rarely used in our daily clinical practice for patients with limited life expectancy (<3 years) due to competing comorbid illness, and for patients with severe dementia who may be overtreated if given combination therapy. For those who decide to start androgen-deprivation therapy alone as systemic therapy in metastatic castration-sensitive prostate cancer patients with better perspective, the guide would be to observe PSA response closely and consider additional treatment if PSA levels do not decline to less than 0.2 ng/ml after 6 to 8 months. Such patients are most likely to have early progression to metastatic castration-resistant prostate cancer and shortened survival with androgen-deprivation therapy alone. For patients who do not have high-volume or high-risk disease, there will still be a dilemma about upfront use of apalutamide or enzalutamide or whether subsequent therapy should be applied if they develop metastatic castration-resistant prostate cancer.

Conclusion

Clinicians’ decisions are usually supported by the type of clinical presentation (symptomatic vs mild or asymptomatic disease), the site of metastases (visceral vs nonvisceral), the presence of significant co-morbidities, the safety of the drug and its potential interactions with other medications. Docetaxel is a good therapy option for the fit mCSPC patients, especially in countries with limited resources.

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Sažetak

U KOJIH BOLESNIKA PRIMIJENITI HORMONSKU TERAPIJU + DOCETAKSEL

M. Gamulin, M. Bebek i M. Gnjidic

Uvođenje kemoterapije docetakselom je dovelo do unaprijedjenja ishoda liječenja u bolesnika s metastatskim senzitivnim rukom prostate te je dodatak docetaksela postao standard liječenja što je temeljeno na rezultatima studija CHAARTED, STAMPEDE, grane C i GETUG-AFU 15 studiji te nakon toga učinjene meta analize. Bolesnici s visokim volumenom bolesti (definicija po CHAARTED studiji) i visokog rizika (definicija prema LATITUTDE studiji), koji imaju dobar performance status i koji su pogodni za kemoterapiju, imaju najviše koristi od dodatka docetaksela androgenoj deprivacijskoj terapiji. Rezultati TITAN studije su pokazali aktivnosti apalutamida u istoj indikaciji. Ipak, prediktivni biomarkeri još uvijek nedostaju. Postoje jasni dokazi o koristi u ukupnom preživljenju od abiraterona, apalutamida i enzalutamida u bolesnika s bolesti visokog volumena koji nisu pogodni za kemoterapiju, kao i za bolesnike s bolesti niskog volumena. Kliničke studije će pokazati mjesto za trostruku terapiju u kliničkoj praksi. Prije objave rezultata novih kliničkih studija, liječnici trebaju temeljiti svoje odluke na temelju procjene rizika i koristi svakog trenutnog pristupa i razmotriti druge parametre poput troškova liječenja, dostupnosti skrbi te preferencije bolesnika.

Ključne riječi: Hormon osjetljivi rak prostate, Docetaksel, Inhibicija androgenih receptora, Visoki volumen, Visoki rizik