Asian Journal of Andrology (2016) 18, 444–445

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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Use of early chemotherapy for hormone-sensitive prostate cancer: time for CHAARTED

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Asian Journal of Andrology (2016) **18**, 444–445; doi: 10.4103/1008-682X.164920; published online: 27 October 2015

CHAARTED was an ECOG-led phase III trial looking at early chemotherapy with the use of docetaxel in addition to androgen deprivation therapy (ADT) versus ADT alone in hormone-sensitive prostate cancer. The positive results of the trial showing marked improvement in overall survival in those who received chemotherapy with ADT have revolutionized the treatment of metastatic castration-sensitive prostate cancer. In addition to overall survival, secondary endpoints such as time to castration resistance, PSA response were also significant for the patients who received early chemotherapy.

Chemotherapy with docetaxel has long been held a standard of care option for men with metastatic castration-resistant prostate cancer (mCRPC), given the overall survival benefit seen with TAX-327[1] and SWOG-9916[2] trials. Later drug approvals of androgen-signaling targeted agents such as abiraterone acetate and enzalutamide were based on improvement in overall survival as well as in both the postdocetaxel and predocetaxel mCRPC settings. The ECOG 3805 CHAARTED (ChemoHormonal Therapy *vs* Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial seeks to determine whether use of early chemotherapy in addition to the known standard of care ADT option would be superior to ADT alone.[3] This was a US-based trial that included 790 men with metastatic hormone-sensitive prostate cancer, who were randomized to ADT and 6 cycles of docetaxel (standard dose of 75 mg m^{-2}) (n = 397) versus ADT alone (n = 393) with a well-balanced patient demographic characteristic between both groups, with a median age of 64 and 63 years, respectively, for the combination versus ADT alone group, with majority of the patients (around 70%) having ECOG performance of 0. The use of prior adjuvant ADT was allowed with a duration of <2 years and progression occurring >1year after therapy. The trial utilized an intent-to-treat analysis with an 80% power to detect an improvement of 33% in overall survival between the combined versus ADT alone arm. The primary endpoint was met with a median overall survival of 57.6 months in the combination arm versus 44 months in the ADT arm although seemingly driven by the high-volume disease subgroup of patients with median overall survival of 49.2 months for the combination versus 32.2 months for the ADT alone arm. All the secondary endpoints also favored the combination versus the ADT alone arm as well, including the median time to development of castration-resistant disease (20.2 months *vs* 11.2 months), time at which undetectable PSA level at <0.2 ng ml^{-1} was achieved at 1 year (27.7 months *vs* 16.8 months), and time until clinical progression was seen (33 months *vs* 19.8 months), all $P < 0.001$. Most of the patients (86%) assigned to the docetaxel arm were able to complete all 6 cycles of therapy with toxicities expected of chemotherapy, albeit with one toxic death occurring. Of note, patients did not receive prednisone as was done with the mCRPC trials and patients were stratified according to the volume of metastases with high-volume of metastases, defined as having visceral metastases or ≥4 bone lesions of which one had to be beyond the vertebral or pelvic bone, comprised 66.2% in the combination group and 63.6% in the ADT group, whereas low-volume metastases consisted only about a third of all patients in both arms.

The results of the CHAARTED trial was unprecedented but was wrought with some controversy since an earlier French trial (GETUG AFU 15) was reported showing no benefit to use of early chemotherapy in the same hormone-sensitive population of patients.[4] However, there were marked differences in the French compared to the ECOG CHAARTED trial, with the French trial enrolling less patients overall (n = 385 *vs* n = 790 in the ECOG trial), more low-volume or intermediate-risk disease patients (around 77%), less high-volume metastases patients (about 52% *vs* 65% in the ECOG CHAARTED), gave more cycles of chemotherapy (up to 9 cycles *vs* 6 cycles in the ECOG trial), with four treatment-related deaths in the combination arm, and while progression-free survival was indeed significant (22.9 months for the combination *vs* 12.9 months, P = 0.005), it failed to show improvement in overall survival (58.9 months for the combination *vs* 54.2 months for ADT alone, P = 0.955). This has brought on the initial controversy of whether the standard of care should change for the treatment of metastatic castration-sensitive prostate cancer.[5] Indeed, one of the hallmarks of success in the prechemotherapy mCRPC trials as a secondary endpoint was the protracted period when chemotherapy had to be initiated. The median time to initiation of chemotherapy with abiraterone acetate in the COU-AA-302 trial was 25.2 months compared to prednisone that was 16.2 months,[6] whereas the median time to initiation of chemotherapy was 28 months for enzalutamide in the PREVAIL trial compared to only 10 months in the comparator placebo arm.[7] The results of this trial and the recently positive STAMPEDE

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trial[8] have further solidified the stance of early chemotherapy, and given less availability or use of novel anti-androgen targeted agents in the post-GETUG AFU 15 trial may have further compromised the survival outcomes. STAMPEDE was a multi-arm, multi-stage trial that explored various combination arms but the docetaxel with ADT as well as zoledronic acid arm was reported at ASCO 2015.[8] This study enrolled both nonmetastatic, locally advanced as well as metastatic hormone-sensitive patients and most of the overall survival benefit resides in the metastatic population of patients (so-called M1 patients) with the addition of docetaxel and zoledronic acid (not zoledronic acid alone) to ADT yielding a 5-month improvement in overall survival that was statistically significant ($P = 0.02$).

The use of early chemotherapy yielded unprecedented results in the treatment landscape of metastatic prostate cancer. It is yet unclear whether the benefit lies mainly in the high-volume disease patients and whether it is truly the volume of disease, rather than biology of disease that drives this difference. It remains important to note that *de novo* metastatic disease remains to be an uncommon presentation (about 4%), and the results of the CHAARTED trial may not necessarily apply to men who progress to metastatic disease from an earlier localized disease presentation. How the disease biology changes upon early initiation of chemotherapy remains unknown. While the ECOG CHAARTED trial does not address the question of optimal sequencing, some provocative observation of retrospective review of sequencing with docetaxel followed by abiraterone and vice-versa shows that outcomes may be better with initial chemotherapy followed by abiraterone than the reverse sequence.[9] Ultimately, patients presenting with metastatic disease who correspond to that of high-volume patients as in the CHAARTED trial warrants consideration and offering of early docetaxel chemotherapy with ADT.

COMPETING INTERESTS

The author declared no competing interests.

REFERENCES

1 Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; 351: 1502–12.
2 Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, *et al*. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; 351: 1513–20.
3 Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, *et al*. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015; 373: 737–46.
4 Gravis G, Fizazi K, Joly F, Oudard S, Priou F, *et al*. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013; 14: 149–58.
5 Fizazi K, Jenkins C, Tannock IF. Should docetaxel be standard of care for patients with metastatic hormone-sensitive prostate cancer? Pro and contra. *Ann Oncol* 2015; 26: 1660–7.
6 Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, *et al*. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; 368: 138–48.
7 Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, *et al*. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; 371: 424–33.
8 James ND, Sydes MR, Mason M, Clarke N, Dearnaley D, *et al*. Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: first overall survival results from STAMPEDE (NCT00268476). *J Clin Oncol* 2015; 33 suppl: [Abstr5001].
9 Maughan ML, Suzman D, Nadal R, Bassi S, Schweizer M, *et al*. Optimal sequencing of docetaxel and abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2015; 33 suppl: [Abstr252].