

Role of systemic chemotherapy in metastatic hormone-sensitive prostate cancer

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ABSTRACT

Introduction: Patients with metastatic hormone sensitive prostate cancer (mHSPC) have traditionally been treated with androgen deprivation therapy (ADT). Recently, there has been a demonstration of a survival benefit with the addition of docetaxel to ADT from three large randomized controlled trials. This review summarizes these trials, draws comparisons between the trials, and attempts to provide critical evidence-based recommendation on the role of docetaxel in mHSPC.

Methods: Of the two published (GETUG-AFU, Chemo-Hormonal therapy vs. Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer [CHAARTED]) and one presented trial (STAMPEDE) an analysis of the study design, patient characteristics, outcomes, variables, and a critical comparison between the trials was performed for making practice recommendations.

Results: All the three trials demonstrated statistically significant progression free survival with the addition of docetaxel to ADT in mHSPC. However, while CHAARTED trial demonstrated a significant survival benefit with addition of docetaxel to ADT in patients with high volume mHSPC, GETUG-AFU failed to demonstrate statistically significant survival benefit although there was an absolute difference in survival between the two arms, with lower sample size and statistical power compared to CHAARTED. The largest study, STAMPEDE, reported a 22 month survival benefit in patients with M1 disease with statistical significance; with subgroup analysis of high volume and low volume disease patients yet to be reported.

Conclusion: After a careful comparison between the trials, we conclude that systemic docetaxel chemotherapy within 4 months of initiating ADT for metastatic, high-volume HSPC should be considered the standard of care for patients with good performance status.

Key words: Chemotherapy, hormones, prostate cancer

INTRODUCTION

Targeting the androgen pathway has for long been the cornerstone of treatment for metastatic hormone sensitive prostate cancer (mHSPC).^[1-5] This therapeutic intervention can be delivered either by continuous androgen deprivation therapy (ADT) or intermittent ADT or by administering higher doses of antiandrogen monotherapy and by using combined androgen blockade.^[6] Despite these approaches, essentially all patients experience progression to castration resistant

prostate cancer (CRPC), with the median duration of sensitivity to ADT ranging between 24 and 36 months. A survival benefit was demonstrated with docetaxel and prednisone in treating CRPC^[7,8] compared to mitoxantrone and prednisone. Docetaxel's antineoplastic activity has multiple mechanisms of action. It inhibits microtubule depolymerization by binding to β -tubulin and resulting in arrest of the cell cycle in the G(2)M phase and also inhibits the antiapoptotic protein Bcl-2 by induction of Bcl-2 phosphorylation.^[9] Recently, inhibition of the androgen receptor and its downstream genes has emerged as a novel mechanism^[10] providing further preclinical rationale for the use of docetaxel in mHSPC.

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This led to further investigation on the role for docetaxel chemotherapy in HSPC, in order to target androgen independent clones that may be inherently resistant to ADT. Over the last decade, three large randomized trials were launched to explore the benefit of using docetaxel in conjunction with ADT in terms of overall survival (OS), biochemical and clinical progression-free survival: GETUG-AFU 15,^[11] Chemo-Hormonal therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer (CHAARTED)^[12] and STAMPEDE.^[13] This review will summarize the published results from these trials and the role of systemic docetaxel chemotherapy in the mHSPC setting. All studies included patients with either clinically detectable distant or loco-regional metastases.

GETUG-AFU 15

In this first of the three studies^[11] to be reported which evaluated a role for docetaxel chemotherapy in mHSPC stage, 385 men with mHSPC were randomized to receive either ADT alone ($n = 193$) or ADT with docetaxel ($n = 192$) - 75 mg/m² every 3 weeks, up to nine cycles, with the primary endpoint being OS. Patients were enrolled across 29 centers in France and 1 in Belgium between October 2004 and December 2008. The long-term follow-up results were published in November 2015.^[14] Even with long-term follow-up and despite an absolute difference in median OS of 14 months, the benefit did not reach statistical significance (62.1 vs. 48.6 months; hazard ratio [HR]: 0.88; 95% confidence interval [CI]: 0.68–1.14; $P = 0.3$).^[14] However, the biologic progression free survival (HR: 0.73; 95% CI: 0.56–0.94; $P = 0.014$) and radiologic progression free survival (HR: 0.75; 95% CI: 0.58–0.97; $P = 0.030$) were significantly longer in the ADT plus docetaxel arm. Seventy-two serious adverse events were reported in the initial publication in 2013,^[11] with two-third being neutropenia, some with fever/infection. Four treatment related deaths occurred in the ADT plus docetaxel arm, two being neutropenia related, after which granulocyte colony-stimulating factor (G-CSF) was included in the protocol. No further treatment-related deaths occurred after this addition.

This study stratified patients into low, intermediate, and high risk-based on the glass risk criteria,^[15] which includes the location of metastasis (appendicular vs. axial), prostate specific antigen (PSA) <65 ng/ml or greater, Gleason score <8 or greater, and Eastern Cooperative Oncology Group (ECOG) performance status. GETUG-AFU 15 enrolled 22% patients with high risk. Another trial running in parallel, CHAARTED, summarized later stratified patients into high volume disease (defined as the presence of visceral metastasis and/or four or more osseous metastases, with at least one being extra-axial) versus low volume disease for evaluating outcomes of adding systemic therapy in HSPC stage. The high volume disease patients in CHAARTED constituted 65.8%

of the total enrolled patients. To facilitate cross comparison, GETUG-AFU 15 retrospectively recategorized its patients according to CHAARTED criteria, and found 52% of their patients to have high-volume disease. However, even the high volume disease patients did not have a statistically significant OS benefit, the primary endpoint of the study with the addition of docetaxel (39.8 vs. 35.1 months, HR: 0.78; 95% CI: 0.56–1.09; $P = 0.14$).^[14] However, there was a benefit in the progression free survival with the addition of docetaxel to ADT. For low volume disease patients, the median OS was not reached.^[14,16]

CHEMO-HORMONAL THERAPY VERSUS ANDROGEN ABLATION RANDOMIZED TRIAL FOR EXTENSIVE DISEASE IN PROSTATE CANCER

This was a larger study^[12] that enrolled 790 mHSPC patients from July 2006 to December 2012 and randomized them to receive ADT alone or ADT plus docetaxel (75 mg/m² every 3 weeks for 6 cycles). In contrast to the GETUG-AFU 15 study, at the time of planned interim analysis, there was a statistically significant improvement in the primary endpoint of the study, OS with the addition of docetaxel (57.6 months vs. 44.0 months; HR: 0.61; 95% CI: 0.47–0.80; $P < 0.001$). The benefit was more prominent in the subgroup with high volume disease than the overall study population (49.2 vs. 32.2 months; HR: 0.60; 95% CI: 0.45–0.81; $P < 0.001$). The median survival for the low volume group had not been reached at the time of analysis. All secondary endpoints namely - time to castration resistance (20.2 vs. 11.7 months; HR: 0.61; 95% CI: 0.51–0.72; $P < 0.001$), time to clinical progression (33.0 vs. 19.8 months, HR: 0.61; 95% CI: 0.50–0.75; $P < 0.001$), and proportion of patients achieving a decrease in serum PSA to <0.2 ng/ml at 12 months (27.7% vs. 16.8%, $P < 0.001$) also favored the addition of docetaxel.

Approximately 6% of the patients in the combination group had neutropenic fever, and approximately 2% had Grade 3 or 4 infection with neutropenia. Grade 3 diarrhea, stomatitis, motor neuropathy, and sensory neuropathy each occurred at a rate of 1% or less.

STAMPEDE

The largest of the three trials, STAMPEDE^[13], accrued 2962 men from October 2005 to March 2013 with either high-risk localized (24%), node-positive (15%), or mHSPC (61%) to four separate treatment arms: ADT alone, ADT plus zoledronic acid, ADT plus docetaxel, or ADT plus zoledronic acid and docetaxel. The first OS results from the trial were presented at the ASCO 2015 annual meeting. The addition of docetaxel demonstrated significance in both its primary endpoint of OS (77 vs. 67 months; HR: 0.76; 95% CI: 0.63–0.91; $P = 0.003$) and secondary endpoint of failure-free survival (37 vs. 21 months; HR: 0.62; 95% CI: 0.54–0.70; $P < 1 \times 10^{-10}$) in the overall study

population. Subgroup analysis of mHSPC (M1) patients also demonstrated OS benefit with docetaxel (65 vs. 43 months; HR: 0.73; 95% CI: 0.59–0.89; $P = 0.002$) but patients with M0 disease did not appear to derive benefit (HR: 1.01; 95% CI: 0.65–1.56). Addition of zoledronic acid did not confer any survival benefit.

COMPARISON BETWEEN THE TRIALS AND RECENT META-ANALYSIS

The two larger trials, CHAARTED and STAMPEDE, demonstrated survival benefit with the addition of docetaxel to ADT in mHSPC. Patients with high volume disease were found to derive the most benefit in CHAARTED. Median survival for patients with low volume was not reached at the time of analysis. In the GETUG-AFU trial, although there was an absolute difference of 14 months between the ADT plus docetaxel and ADT arms which was comparable to the CHAARTED study, statistical significance was not reached, possibly due to the smaller sample size and lesser statistical power of the study. The largest study, STAMPEDE, reported a staggering 22 month survival benefit in patients with M1 disease but subgroup analysis of high volume and low volume disease patients is yet to be reported.

In the CHAARTED study, patients with high volume disease comprised of 65.8% of the total study population, significantly larger than in the GETUG-AFU study, where they comprised of 47.5%. The median PSA was also twice more in the CHAARTED study in comparison to the GETUG study-reflecting that the CHAARTED patient group as a whole had a worse prognosis disease in comparison to the GETUG group-benefitting from earlier initiation of chemotherapy.^[14]

An important consideration is the difference in the post-trial treatment pattern between the studies, which could be a significant confounding factor. Patient accrual for the GETUG-AFU, CHAARTED, and STAMPEDE studies stopped in December 2008, December 2012 and March 2013, respectively, and newer second line agents with survival benefit (abiraterone, enzalutamide, and cabazitaxel) were available for a larger percentage of patients in the CHAARTED and STAMPEDE studies compared to the GETUG-AFU study. In the CHAARTED trial, the experimental ADT plus docetaxel arm received numerically more active drugs after progression, in comparison to the control ADT arm-cabazitaxel (23.9% and 12.9%), abiraterone and/or enzalutamide (44.1% and 36.2%), and sipuleucel-T (9.2% and 6.6%).^[14] GETUG-AFU, on the other hand, had a much higher percentage of patients receiving salvage docetaxel therapy in comparison with CHAARTED (45.2% vs. 22.5%) possible because no other drug was approved for metastatic CRPC (mCRPC) for many months after December 2008, when the accrual for the GETUG study

closed. With more patients in the control arm receiving salvage docetaxel, early docetaxel likely showed lesser OS benefit in the GETUG study, than it otherwise would have. GETUG-AFU study was therefore, more of a comparison between early and late docetaxel.

A recent meta-analysis of use of docetaxel in HSPC showed that the addition of docetaxel to standard of care improved survival. The HR of 0.77 (95% CI: 0.68–0.87; $P < 0.0001$) translates to an absolute improvement in 4-year survival of 9% (95% CI: 5–14). Docetaxel in addition to standard of care also improved failure-free survival, with the HR of 0.64 (95% CI: 0.58–0.70; $P < 0.0001$) translating into a reduction in absolute 4-year failure rates of 16% (95% CI: 12–19).^[17]

WHO STANDS TO BENEFIT FROM EARLY DOCETAXEL WITH ANDROGEN DEPRIVATION THERAPY IN HORMONE SENSITIVE PROSTATE CANCER?

From the available data, selected subsets of mHSPC stage patients stand to benefit the most from upfront docetaxel with ADT. These include patients with metastatic high volume disease (defined as the presence of visceral metastasis and/or four or more osseous metastases, with at least one being extra-axial). The absolute difference in OS (17 months in CHAARTED and 22 months in STAMPEDE for high volume disease and M1 disease, respectively), was strikingly in favor of initiating early initiation of chemotherapy. In addition, patient typically eligible had an ECOG performance status of 0–2 with most enrolled finally with a functional status of 0–1, and rarely 2.

Data for patients with low volume disease patients for the primary endpoint of OS not mature yet, although the difference in the biochemical progression free survival even for low volume disease patients in the GETUG-AFU study was 18 months (40.9 vs. 22.4, $P = 0.053$) favoring the ADT + docetaxel group.

DISCUSSION ON POTENTIAL CONCERNS

The National Comprehensive Cancer Network while evaluating the survival benefit of early docetaxel in mHSPC in high volume disease and docetaxel plus ADT has now included this intervention as the standard of care for mHSPC high volume disease in the United States. However, this has been delayed in some European countries, until the differences between the GETUG-AFU and CHAARTED trials are resolved. The two major concerns stated are as follows:

1. The results of the GETUG-AFU study are more mature than CHAARTED, which was reported when median follow-up (29 months) was much shorter than reported median OS (44 and 57.6 months in the two arms); results were based on Kaplan–Meier projections, and difference in OS between arms of the CHAARTED study may decrease,

and the HR increase, with further follow-up. Moreover, if docetaxel is truly effective for men with HSPC, it is surprising that the more intense schedule of docetaxel used in GETUGAFU-15 (nine cycles) was not more effective than that used in CHAARTED (six cycles)^[16]

A counterargument at this stage to the above concern would be the results of the STAMPEDE trial, which overwhelmingly supports the results of the CHAARTED trial. Furthermore it's quite likely that the smaller sample size and statistical power of the GETUG study and the lower number of high volume patients enrolled in the study resulted in nonstatistically significant differences in survival with docetaxel

2. Toxicity and exaggeration of benefit in clinical trials compared to routine clinical practice:

Four treatment-related deaths in the GETUG study and one in the CHAARTED study were observed with febrile neutropenia accounting for two of the deaths in the GETUG study. In additionally, 6% of the patients in the combination treatment group developed neutropenic fever in CHAARTED. Considering that clinical trials usually enroll patients that are fitter, satisfy strict inclusion criteria and receive regular monitoring, the concern is that these numbers would be much higher in the real world scenario is realistic. The alternative of just targeting the androgen pathway is well tolerated, has a median duration of response of 1–2 years in patients with metastatic disease.^[18,19] A study performed in Princess Margaret Cancer Center in Canada, found that 9.6% of their patients on 3 weekly docetaxel for mCRPC developed febrile neutropenia compared to 3% reported in the TAX 327 study. The median OS was also 13.6 months compared to 19.3 months as reported in the TAX 327 study.^[20]

Toxicity, undoubtedly therefore is a valid concern, especially when docetaxel is accepted as a standard of care in low- to middle-income countries of if centers delivering care are not experienced and lesser equipped for delivering chemotherapy. Of note, the addition of G-CSF to the protocol in the GETUG study helped mitigate any further occurrences of deaths. But this concern underscores the need for regular monitoring particularly of the neutrophil count, and administration of G-CSF either as primary or secondary prophylaxis against febrile neutropenias; careful patient selection based on performance status and co-morbidities; sound clinical judgement on dosage modifications if required, based on individual toxicity; if the benefit of early docetaxel in mHSPC is to be replicated in routine clinical practice around the world.

CONCLUSIONS AND IMPLICATIONS IN LOW- AND MIDDLE-INCOME COUNTRIES

Systemic docetaxel chemotherapy within 4 months of initiating ADT for metastatic, high-volume HSPC should

be considered the standard of care for patients with good performance status. This new standard of care offers a statistically significant improvement from the previous standard established for treating this stage of disease over seven decades ago and should be rapidly adopted. The percentage of patients presenting with *de novo* metastatic disease is much higher in low- and middle-income countries compared to the western countries, given the limited access to health care.^[21,22] Considering the rise in incidence of prostate cancer in developing countries, a change in practice patterns with an earlier adopting of docetaxel with ADT as the standard of care for mHSPC patients with high volume disease is needed and this requires a greater emphasis on interdisciplinary urological and oncological collaboration during patient management. The degree of such collaborations can vary between regions form well integrated multi-disciplinary team approach to a restrictive referral practice. In order to deliver the fairly large longevity benefit observed in most randomized trials with the addition of chemotherapy to ADT, a greater emphasis on integrative practice approaches is likely to ensure the best outcomes in patient care.

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Conflicts of interest

There are no conflicts of interest.

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