Review Article

STAMPEDEing metastatic prostate cancer: CHAARTing the LATITUDEs

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ABSTRACT

With the emergence of recent landmark trials, the treatment for hormone-sensitive metastatic prostate cancer (hsMPC) is changing from androgen deprivation therapy (ADT) alone to combination therapy. Both, docetaxel chemotherapy and abiraterone in addition to ADT have been extensively studied in well-conducted randomized controlled trials and were shown to improve outcomes. However, this paradigm shift in the treatment has also raised some queries. This mini review reflects upon the four landmark trials and tries to provide some perspective about the decision-making process for the patients with hsMPC.

INTRODUCTION

The management of metastatic prostate cancer has a special place in urology as Charles Huggins, in 1966, won the Nobel Prize in physiology for "Hormone treatment in prostate cancer."[1] For a long time, the treatment of choice for metastatic prostate cancer remained bilateral orchiectomy.[2] However, the procedure came with its own problems of andropause and the psychological trauma of disfigurement. Then came the era of hormonal manipulation using androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone (LHRH) agonists followed by the LHRH antagonists.[3] All of them had a common objective; prolonging cancer-specific survival and overall survival (OS) in patients with metastatic prostate cancer with an efficacy equivalent to castration by bilateral orchiectomy.[2]

The last few years have seen a paradigm shift in the management of hormone-sensitive metastatic prostate cancer (hsMPC). Various treatment modalities that are usually used for castration-resistant prostate cancer (CRPC) were evaluated for hsMPC in multiple landmark trials which led to the accumulation of a large data set that could be analyzed in a relatively short span of time.[4-7] A summary of the major results of the four landmark trials is depicted in Figure 1.

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THE TRIALS – DOCETAXEL WITH ADT

The Systemic Therapy in Advanced and Metastatic Prostate Cancer Evaluation of Drug Efficacy (STAMPEDE) and Chemo Hormonal Therapy versus Androgen Ablation Randomized Trial in Extensive Disease (CHAARTED) trials established docetaxel chemotherapy, in addition to the ADT, as the first-line therapy in metastatic prostate cancer, and opened new avenues for both the clinicians and the patients dealing with metastatic prostate cancer.[4,5]

In the CHAARTED and the STAMPEDE (Arm C, hereby referred to as STAMPEDE alone) trials, the hazard ratio (HR) for OS on adding six cycles of docetaxel to ADT was 0.61 and 0.78, respectively.[4,5] However, the absolute survival in months differed in both the trials, i.e., 71 months and 81 months (STAMPEDE) versus

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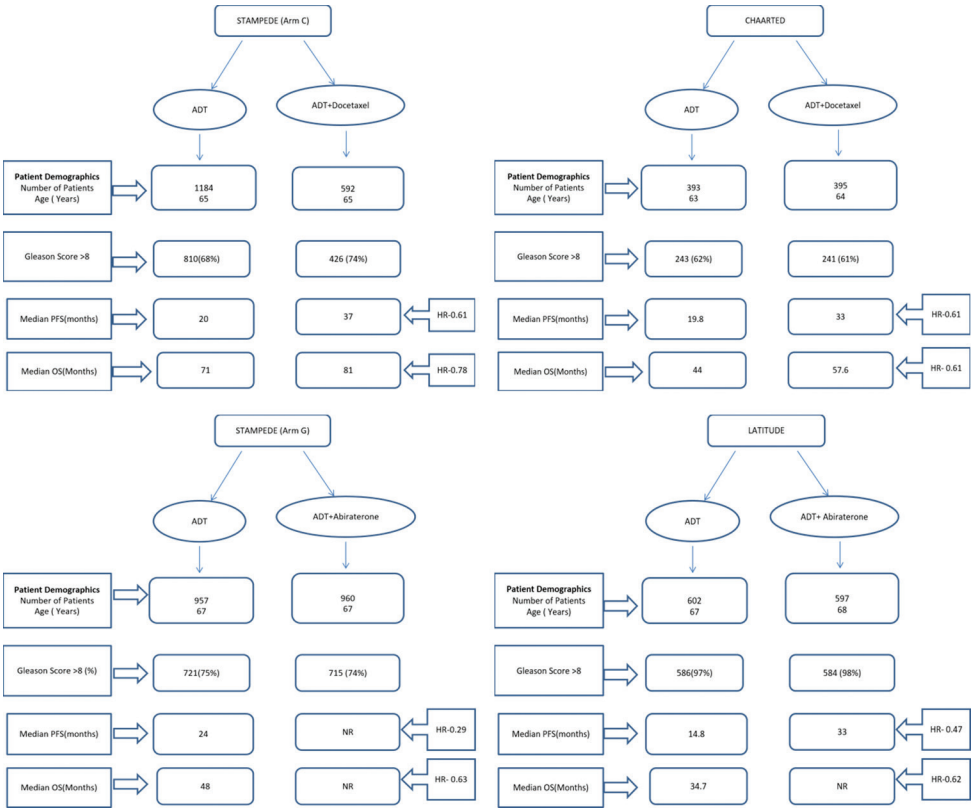

Figure 1: Summary of the trials on combination therapies in metastatic hormone-sensitive prostate cancer. ADT: Androgen deprivation therapy, PFS: Progression-free survival, OS: Overall survival, HR: Hazard ratio, NA: Not available, *CHAARTED distributed patients into high volume and low volume in which high volume of metastases was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis

44 months and 57.6 months (CHAARTED), respectively.[4,5] This stark difference resulted from the difference in the patient population evaluated. The STAMPEDE trial also included M0 patients, which comprised almost 39% of the total population. Thus, in the same trial, on analyzing the subgroup of patients with metastatic disease alone, the median OS was found to be 45 months and 60 months, in the ADT and the ADT + docetaxel, respectively.[4,5]

Based on these trials, Botrel *et al.* published a meta-analysis of three most prominent trials (GETUG-15, STAMPEDE, and CHAARTED) comprising of 2264 patients with hsMPC.[8] They found that the patients who received the chemohormonal therapy had a longer clinical progression-free survival (PFS) interval (HR = 0.64; 95% confidence interval [CI] = 0.55–0.75; $P < 0.00001$), and no heterogeneity ($\chi^2 = 0.64$; df = 1 [$P = 0.42$]; $I^2 = 0\%$).[8] The biochemical PFS (bPFS) was also longer in patients treated with ADT plus docetaxel (HR = 0.63; 95% CI = 0.57–0.69; $P < 0.00001$), also with no heterogeneity noted ($\chi^2 = 0.48$; df = 2 [$P = 0.79$]; $I^2 = 0\%$).[8] Finally, the combination of ADT with docetaxel showed a superior OS compared with ADT alone (HR = 0.73; 95% CI = 0.64–0.84; $P < 0.0001$), with moderate heterogeneity ($\chi^2 = 3.84$; df = 2 [$P = 0.15$]; $I^2 = 48\%$).[8] Tests for heterogeneity conclude consistency or inconsistency of the studies included in meta-analyses and a value of $I^2 = 0\%$ indicates no observed heterogeneity.

The GETUG 15, although a fairly well-conducted trial, has been criticized on a few accounts. There was a difference in the number of cycles of chemotherapy given, i.e., 9 cycles in GEUTG 15 instead of 6 cycles in CHAARTED and STAMPEDE and the subpopulation of patients with Gleason Score (GS) >8 in GETUG 15 was smaller than that included in CHAARTED and STAMPEDE trials[4,5,8,9] Based on these differences, even if the GETUG-15 trial is excluded from the final OS analysis, the results of the meta-analysis still remained favorable towards combined chemohormonal regimen (HR = 0.68; 95% CI = 0.58–0.80; $P < 0.00001$), with no heterogeneity ($I^2 = 9\%$).[8,9] Also, in the same meta-analysis, on performing a subgroup evaluation of patients with high-volume disease, the use of the combination therapy resulted in an increase in OS (HR = 0.67; 95% CI = 0.54–0.83; $P = 0.0003$).[8]

On evaluating the data on adverse events and severe toxicity (Grade 3), it was found that the group receiving the combined therapy with docetaxel had higher rates of neutropenia, febrile neutropenia, and fatigue.[8] The authors concluded that the combination of ADT with docetaxel improved the clinical PFS, bPFS, and OS in patients with hsMPC. A superior OS was seen, especially in patients with metastatic and high-volume disease in this meta-analysis, echoing the result of previous two positive trials, i.e., CHAARTED and STAMPEDE.[4,5,8]

THE TRIALS – ABIRATERONE WITH ADT

The recently published LATITUDE and STAMPEDE trials (Arm G) have explored the role of abiraterone in combination with prednisolone in addition to ADT.[6,7] Both these trials were designed to determine if newly diagnosed high-risk hsMPC cancer patients benefit from the addition of abiraterone and low-dose prednisone to ADT.[4-7] The LATITUDE study included 1,199 patients at 235 sites in 34 countries who were randomized to receive either ADT plus abiraterone (1000 mg daily) plus prednisone (5 mg daily) (treatment arm – 597 patients) or ADT plus dual placebos (control arm – 602 patients).[6]

The study found that the treatment arm had an improvement in both the OS and the PFS. In the treatment arm, the risk of death was reduced by 38% as compared to the control arm (HR = 0.62; 95% CI = 0.51–0.76, $P < 0.0001$), while the risk reduction in the terms of progression was 53% as compared to a placebo (HR = 0.47; 95% CI = 0.39–0.55, $P < 0.0001$).[6] The median OS was significantly longer in the treatment arm than that noted in the control arm (not reached vs. 34.7 months) and the median length of radiographic PFS was 33.0 months in the treatment arm as compared to 14.8 months in the control arm.[6] As the difference in the OS between the treatment arm and the control arm was statistically significant at the time of the first interim analysis, the independent Data and Safety Monitoring Committee recommended unblinding of the study and allowed for the crossover from the control arm to the treatment arm.[6]

The results of STAMPEDE (arm G) trial mirrored the findings of the aforementioned LATITUDE trial. It included a total of 1,917 patients and showed an improvement of 37% in the OS (HR = 0.63; 95% CI = 0.52–0.76, $P < 0.001$).[7] It also found that the combined androgen blockade (CAB) in addition to abiraterone could significantly reduce the number of deaths from 262 in the ADT alone group to 184 in the combination treatment group.[7] Additionally, for patients with metastatic prostate cancer, the 3-year survival was 83% in the abiraterone group as compared to 76% in the ADT group, with a HR of 0.61. The HR for failure-free survival in patients with nonmetastatic disease was 0.21, which is also remarkable.[7]

Looking closely at the data from the LATITUDE trial, a subpopulation analysis revealed that the results favored the abiraterone arm, although they could not reach a statistical significance in the Asian (HR = 0.73, 95% CI = 0.42–1.27), the Western European populations (HR = 0.75, 95% CI = 0.51–1.09), and rest of the world's population (HR = 0.70, 95% CI = 0.45–1.09).[6] On the other hand, the radiographic PFS was statistically significantly different even in these subpopulations also. Will these results have implications in choosing abiraterone therapy, especially in Asian and Western European populations? Probably, a separate follow-up needs to be done to look whether the benefits, as claimed by the LATITUDE group, actually materialize in these subpopulations also.

Rydzewska *et al.* conducted a systematic review of the LATITUDE and the STAMPEDE trials (Arm G) and found a highly significant 55% reduction in the risk of clinical/radiological PFS for the abiraterone with ADT arm as compared to ADT alone. Abiraterone addition provided a 14% absolute improvement in 3-year OS compared to the 8% absolute improvement noted with docetaxel addition.[10] However, this crude comparison did not take into account the different time frames and different patient populations studied across these trials.

SUBPOPULATION MOST BENEFITTED

In the pooled analysis of the patients with low-volume of disease burden, the OS was similar for patients who received ADT plus docetaxel as compared to those receiving ADT alone. Similar results were found on the addition of abiraterone to ADT in both the LATITUDE and the STAMPEDE trials (Arm G) for the patients with low GS (GS < 8).[6,7] The HR for patients with GS < 8 in LATITUDE was 0.62 with 95% CI of 0.18–2.11 and in STAMPEDE (Arm G) trial, the HR was 0.76 with 95% CI of 0.48–1.23.[6,7] However, the subset analysis of high volume disease patients included in the CHAARTED and the STAMPEDE trial reported the greatest improvement in OS,[4,5] this is similar to that noted in the LATITUDE population. The only simple conclusion that can be drawn from these comparisons is that a newly diagnosed high-risk (GS ≥ 8 or high metastatic burden) metastatic prostate cancer patient should be offered upfront docetaxel or abiraterone in addition to ADT.

Tucci *et al.* performed an exploratory analysis of treatment efficacy according to the disease volume.[11] The study had limited statistical power, thus they were unable to demonstrate a significant interaction between disease volume and treatment efficacy.[11] They further stated that this absence of significant interaction does not preclude the addition of docetaxel to ADT in patients with low-volume metastatic disease.[11] However, with the currently available evidence, no definitive statement can be made about the interaction between docetaxel efficacy and disease volume. The EAU 2017 guidelines also recommend ADT + docetaxel as the first-line therapy for M1 patients irrespective of their disease volume.[12]

FACTORS THAT WILL AFFECT THE CHOICE

These trials opened new options for patients with metastatic prostate cancer [Table 1].[6,7] While docetaxel acts on the cancer cells and is tumoricidal, abiraterone is an androgen

Table 1: Comparison of abiraterone and docetaxel in practice

Parameter	Docetaxel	Abiraterone
PS	Good PS	Can be used in poor PS
Hypertension	-	+
Diabetes mellitus	-	+
Hypokalemia	-	+
Neuropathy	+	-
Neutropenia	+	-
Treatment duration	Finite	Prolonged
Oral versus injectable	Injections	Oral
Treatment cost	Less	More

+=Present, -=Absent, PS=Performance status

biosynthesis inhibitor which is likely to be tumorostatic. However, advocates of abiraterone incriminate an active D4A metabolite of abiraterone to have its antitumor effects.[13] This marked improvement in survival as noted with the addition of abiraterone comes at the cost of side effects, namely hypertension and hypokalemia, as noted in the treatment arms of both the LATITUDE and the STAMPEDE (Arm G) trials.[6,7]

There is some evidence from the available literature that the efficacy of docetaxel is impaired when used after novel androgen receptor-targeted therapy such as abiraterone and enzalutamide.[14-16] Thus, the advocates of docetaxel chemotherapy promote its use early in the treatment of prostate cancer, prior to the use of androgen receptor-targeting agents. This might also prevent the accumulation of castration-resistant cell subpopulation and thus prolong the time to development of CRPC.[17]

The overall treatment cost of docetaxel therapy is lower and it is widely available. The treatment is for a finite duration and 6 cycles can be completed within 4 months' time. Further, comparing the toxicity, docetaxel treatment appears safer and is associated with a 20% increase in Grade ≥3 toxicity as compared to ADT, which is mostly neutropenia and febrile neutropenia.[5,8]

If prescribed upfront in CAB, abiraterone is to be taken till the time of progression, representing a median treatment duration of ~ 2 years.[7] This leads to a considerable cost burden on the patient, especially in a country like ours, where there is poor social support to the elderly and the insurance system is still in its infancy. A cost-effectiveness analysis comparing the costs of all the agents used for prostate cancer found a major difference in the cost of administration of abiraterone for 8 months ($43,216) versus 9.5 cycles of docetaxel ($16,235).[18] This, in effect, will lead to one of the difficult problems of poor treatment compliance with abiraterone, which is much more prevalent in the Indian setup. Further, there is an increase in Grade ≥3 adverse effects by 15% as noted in the LATITUDE and by 14% as noted in the STAMPEDE (Arm G) trials than that noted for ADT alone, mostly hypertension, hypokalemia, and liver disease.[6,7] Dose reduction or treatment interruptions were reported in both the trials. In the STAMPEDE (arm G) trial, 20% of patients had treatment interruption.[7]

Another very important consideration in deciding treatment approach is, quality of life (QoL) provided by the treatment modality. At the present time, QoL data are not available from these trials. However, as the data matures and QoL data becomes available, it shall become one of the prime drivers in deciding the treatment patterns in hsMPC. Only one study has reported QoL data comparing docetaxel + ADT versus ADT alone. This study suggest that docetaxel + ADT does not confer a long-term negative impact on QoL for hsMPC.[19]

THE QUERIES

With the abundance of therapeutic options available for the treatment of patient with hsMPC, a new set of queries arise. What is the standard of care for patients with hsMPC? Which subset of patients shall benefit with docetaxel chemotherapy + ADT versus ADT alone? Which subset of patients shall benefit with abiraterone therapy + ADT versus ADT alone? Which subset of patients shall benefit with docetaxel + ADT versus abiraterone + ADT?

THE FUTURE

A randomized head-to-head trial (PEACE-1 Phase III trial [ClinicalTrials.gov identifier: NCT01957436]) looking into these two therapeutic arms shall identify the patient subset which is the best fit for either of the treatments [Table 2]. A novel treatment protocol involving addition of both docetaxel and abiraterone will be the next stop for the urologist and medical oncologists. This will take some years to materialise, as only the second phase of the PEACE-1 trial will provide data on ADT plus docetaxel plus abiraterone by 2020.[10] Furthermore, as enzalutamide has been shown to have a similar clinical effect on androgen signaling in CRPC as abiraterone, the ENZAMET trial (NCT02446405) of enzalutamide plus ADT,[20] which has recently completed its accrual, and the ARCHES trial (NCT02677896), which is still recruiting,[21] both of which are stratified by docetaxel use, will further augment our knowledge of such "triplet therapy." Also, the ARASENS trial (NCT02799602) will provide evidence about the effects of darolutamide in men receiving ADT plus docetaxel as their standard of care.[22] However, results of ARCHES and ARASENS are unlikely to be available in the near future.

CONCLUSIONS

There is a paradigm shift in the treatment of hsMPC based on the recently published landmark trials. Now, level 1

Table 2: Details of ongoing studies on hormone-sensitive metastatic prostate cancer

Study	Groups	Patients enrolled	Primary end point	Current status
PEACE-1	ADT ± docetaxel versus ADT + abiraterone ± docetaxel (±local RT)	916	PFS, OS	Recruiting
ENZAMET	ADT + enzalutamide versus ADT+ antiandrogen	1100	OS	Ongoing
ARCHES	ADT ± enzalutamide	1100	PFS	Recruiting
ARASENS	ADT + docetaxel±darolutamide	1300	OS	Recruiting
TITAN	ADT ± apalutamide	1000	PFS, OS	Recruiting
STAMPEDE (Arm J)	ADT ± abiraterone + enzalutamide	1800	OS	Ongoing

ADT=Androgen deprivation therapy, PFS=Progression-free survival, OS=Overall survival, RT=Radiotherapy

evidence is available and all newly diagnosed metastatic prostate cancer patients may be offered either docetaxel or abiraterone in addition to ADT. A number of patient-related and treatment-related factors shall affect the choice between these two treatment modalities. With new randomized controlled trials underway, we may be better able to define the best strategy of managing hsMPC.

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