Original Article

Do Indian men have similar oncological outcomes with abiraterone plus androgen deprivation therapy in the setting of metastatic hormone-sensitive prostate cancer? A prospective observational study

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ABSTRACT

Introduction: Combination of abiraterone with androgen deprivation therapy (ADT) has better survival outcomes than ADT alone in metastatic Hormone-sensitive prostate cancer (mHSPC) in the Western population. In this prospective (Clinical Trials Registry-India [CTRI] registered) observational study, we present the comparative oncological outcomes of ADT alone and ADT + abiraterone in Indian patients, which is not available currently.

Methods: This study (CTRI-number-CTRI/2020/07/026545) included newly diagnosed mHSPC patients from January 2020 to June 2023 in a tertiary care hospital, urology department. Patients fulfilling inclusion criteria were advised ADT with abiraterone (A + ADT), and those not affording received ADT monotherapy (ADT). The primary endpoint was overall survival (OS). Secondary outcomes included prostate-specific antigen (PSA) decline >90%, radiographic progression-free survival (rPFS), and PSA progression-free survival (pPFS).

Results: Out of 278 patients with mHSPC, 163 patients were excluded and 115 were analyzed (ADT = 40 vs. A + ADT = 75). After a median follow-up of 20.3 months, 11 of 40 (27.5%) in ADT-only arm and 15 of 75 (20%) in ADT + abiraterone arm had died (Hazard-ratio of death 0.72; 95% confidence interval 0.68–0.88; $P < 0.001$). A PSA decline of >90% was seen in 85% in the ADT alone group and 93.3% in the ADT + abiraterone group. Significantly better outcomes of the ADT + abiraterone were seen in the secondary endpoints of rPFS ($P < 0.001$) and pPFS ($P < 0.001$). The OS benefit was 28% reduction in risk of death in our study versus 37% and 38% in STAMPEDE and LATITUDE, respectively. pPFS and rPFS were also poorer in Indian subsets.

Conclusions: Abiraterone with ADT improves OS, PSA response, rPFS, and pPFS in the Indian population akin to the Western data but with poorer OS, rPFS, and PSA progression-free survival on comparison.

INTRODUCTION

Androgen deprivation therapy (ADT) is the foundation of the treatment of metastatic hormone-sensitive prostate cancer (mHSPC). The treatment that was pioneered and championed by Charles Higgins and Clarence Hodges has been used for more than 80 years.

Over the last decade, the addition of abiraterone to ADT has shown an improvement in the oncological outcomes of hormone-refractory prostate cancer. Extrapolating these results to hormone-sensitive prostate cancer, the LATITUDE and the STAMPEDE trials, gave concrete evidence of better oncological outcomes of combining

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ADT with abiraterone in a mHSPC setting.[1,2] This is reflected in the European Association of Urology (EAU) 2023 guidelines recommendation for starting a combination regimen in treatment naïve metastatic prostate cancer patients. However, none of these studies included the Indian population and the effect of combination therapy in the Indian population is unknown. We conducted the present study to compare the oncological outcomes of combination therapy (ADT + abiraterone) with ADT alone in mHSPC among the Indian population.

MATERIALS AND METHODS

Study design and conduct

This prospective observational study was done in a tertiary care hospital in eastern India. The study protocol was approved by the Institute Ethics Committee (Ref Number: T/IM-NF/Urology/19/66 February 10, 2020) and Clinical Trials Registry-India (CTRI) Registered (CTRI/2020/07/026545). In this study, we reviewed the prospectively collected hospital records of new mHSPC patients treated at our center from January 2020 to June 2023. The study was conducted according to the principles of the Declaration of Helsinki. The requirement of individual patient consent was waived off by the institutional ethics committee. All the authors had access to the original collected data and participated in the drafting of the manuscript.

Study population

Treatment naïve patients having histological confirmation of prostatic adenocarcinoma by extended template Transrectal Ultrasonography (TURS) biopsy and metastasis detected by contrast-enhanced computed tomography (CECT) of the chest, abdomen and pelvis along with a bone scan/Ga68 PSMA positron emission tomography (PET) CT were considered for the study. All patients with an Eastern Cooperative Oncology Group performance status 0–2 were included in the study. Inclusion criteria were men who fulfilled at least two of the three high-risk prognostic factors (GS ≥8, ≥3 lesions on bone scan, and visceral metastases, excluding lymph node metastasis).[1] Patients with variant histology or whose data were incomplete were excluded. Patients who received any other form of prostate cancer treatment other than ADT/ADT + abiraterone were also excluded. Patients with at least 3 months of follow-up were considered for the analysis.

Outcomes

The primary outcome of overall survival (OS) was defined as the time from treatment initiation to death due to any cause. Secondary outcomes were prostate-specific antigen (PSA) decline of >90% compared to baseline, PSA progression-free survival (pPFS), defined as the time from initiation of treatment to PSA progression (prostate cancer working group [PCWG]-2 criteria),[3] and radiological progression-free survival defined as the time from initiation of treatment to radiographicprogression (RECIST ver. 1.1 for measurable disease and PCWG-2 criteria for bony metastasis).[3,4]

Treatment

Treatment was started within 3 months of diagnosis. Patients prescribed combination treatment received ADT with abiraterone acetate (1000 mg) + prednisolone (5 mg OD) once a day continuously (treatment arm). Patients who could not afford abiraterone constituted the control arm (ADT arm). ADT consisted of either surgical castration (bilateral orchidectomy) or medical castration (luteinizing hormone–releasing hormone [LHRH] analog/LHRH antagonist) based on the patient's preference and financial constraints. Androgen receptor blockers were not considered for standalone therapy but were allowed in combination with gonadotropin-releasing hormone (GnRH) analogs to prevent the flareup phenomenon in susceptible individuals. The dose of GnRH analogs and GnRH antagonists depended on the degree of response, namely, reduction in serum testosterone below the castration level (<50 ng/dl at 1 month after starting the treatment). Patients with impending spinal compression could be started on GnRH antagonists initially for immediate relief and could be shifted to GnRH analogs once the patient was stable. Treatment interruptions for toxicity were allowed. Hence, the treatment arm constituted patients who received either surgical or medical castration along with abiraterone while the control arm constituted patients who received surgical or medical castration alone.

Outcome assessment and data collection

Baseline demographics, clinical and pathological characteristics, and serum PSA values were noted from the institution's cancer database. Radiological investigations were retrieved from Picture Archiving and Communication System (PACS)_and reviewed by a radiologist. Patients who had undergone CECT chest, abdomen and pelvis and a bone scan at baseline were followed up with the same investigations. Similarly, patients initially evaluated with Ga68 PSMA PET CT were followed with the same study.

ALL patients were followed up clinically every 3 months from the start of treatment as per the EAU guidelines. This consisted of clinical history, physical examination, serum PSA estimation, and serum testosterone estimation. The findings were prospectively recorded in the institutional database. Radiological investigations were repeated for radiological progression in case of clinical indication or PSA progression. The PCWG-2 criteria were considered for defining PSA progression.

Data management and statistical analysis

Categorical data were represented as frequency (percentage), while quantitative data were presented as mean (standard deviation) for normal distribution or median (range) for skewed distribution. Student's *t*-test was used for continuous variables with normal distribution and the Mann–Whitney *U*

test for skewed distribution. The Chi-square ($\chi 2$) test/Fisher's exact test was used for categorical variables. Time-to-event analysis was done, and the Cox proportional hazards model was used to estimate the hazard ratio. A log-rank test was used to compare the time to event endpoints. Statistical significance was set at $P < 0.05$. SPSS® ver. 25 software (IBM, Chicago, IL, USA). was utilized for data analysis.

RESULTS

Baseline characteristics

Two hundred and seventy-eight patients were diagnosed with mHSPC between July 2020 and January 2023. Data of 163 patients were incomplete or the patients were lost to follow-up. Out of the remaining 115 patients included in the analysis, 40 had received ADT alone (cohort 1) and 75 had received ADT + abiraterone (cohort 2). The baseline demographic and clinicopathological data are shown in Table 1 and the key outcomes measures are shown in Table 2.

The median age at presentation in group 1 was 73 (56–89) years and 70 (59–90) years. ISUP grade group 4 was the most common presentation followed by grade groups 3, 5, 2, and 1 in both the groups. Bone was the most common metastatic site in both the groups followed by nonregional lymph nodes and other visceral metastasis. GnRH analogs were the most common mode of ADT in both groups followed by bilateral orchidectomy and GnRH antagonists in that order.

Table 1: Baseline characteristic of the two groups

Parameter	ADT alone	ADT + abiraterone
Patients (*n*)	40	75
Age (years), median (range)	73 (56–89)	70 (59–90)
Serum PSA (ng/mL), median (range)	78.5 (11.8–1189)	98.3 (37.2–1788)
BMI (kg/m^2), median (range)	23.7 (19.2–32.7)	26.4 (18.6–34.8)
ISUP grade group		
1	2 (5)	6 (8)
2	7 (17.5)	8 (10.6)
3	8 (20)	21 (28)
4	15 (37.5)	32 (42.6)
5	8 (20)	8 (10.6)
Comorbidities		
Diabetes mellitus	9 (22.5)	23 (30.6)
Hypertension	13 (32.5)	37 (49.3)
Coronary artery disease	1 (2.5)	8 (10.6)
Stroke	0	2 (2.6)
COPD	5 (12.5)	9 (12)
Site of metastasis at baseline		
Nonregional lymph nodes	14 (35)	43 (57.3)
Bony metastasis	30 (75)	54 (72)
Visceral metastasis	8 (20)	14 (22.6)
Metastatic tumor volume (CHAARTED criteria)		
Low volume	25 (62.5)	54 (72)
High volume	15 (37.5)	21 (28)
ADT received		
Bilateral orchidectomy	8 (20)	13 (17.33)
GnRH agonist	31 (77.5)	60 (80)
GNRH antagonist	1 (2.5)	2 (2.6)

ADT=Androgen deprivation therapy, COPD=Chronic obstructive pulmonary disease, BMI=Body mass index, PSA=Prostate-specific antigen, ISUP=International Society of Urological Pathology, GNRH=Gonadotrophic-releasing Hormone, CHAARTED=Chemohormonal therapy versus Androgen Ablation Randomizes Trial for Extensive Disease in prostate cancer trial

Primary endpoint-overall survival

The analysis was done after an overall median follow-up of 20.3 months [Figure 1]. There were 26 deaths in total of which 11 (27.5% of group 1) were in group 1 and 15 (20% of group) were in group 2. The OS at 2 years was 70% in group 1 and 85% in group 2. The relative risk of death was 28% lower in group 2 than in group 1 (hazard ratio, 0.72:95% confidence interval (CI), 0.68–0.88; $P < 0.001$).

Secondary endpoints

Prostate-specific antigen decline >90%

A PSA decline of >90% (nadir compared with baseline) was seen in 34 of 40 (85%) in the ADT alone group and 70/75 (93.3%) in the ADT + abiraterone group. The difference of 8.3% was not statistically significant ($P = 0.28$).

Prostate-specific antigen progression-free survival

The median PSA pPFS was 8.9 months in group 1 and 21.7 months in group 2, with a 75% lower risk of PSA progression compared to group 1 (hazard ratio, 0.25:95% CI, 0.20–0.36; $P < 0.001$) [Figure 2].

Radiological progression-free survival

The median radiological pPFS was 17.4 months in group 1 and 25.3 months in group 2 with a 60% lower risk of radiological progression compared to group 1 (hazard ratio 0.40;95% CI, 0.34–0.68; $P < 0.001$) [Figure 3].

Adverse events

Two patients in the ADT + abiraterone group had new onset of diabetes while on treatment and were managed by oral hypoglycemic agents. No new-onset diabetes was seen in

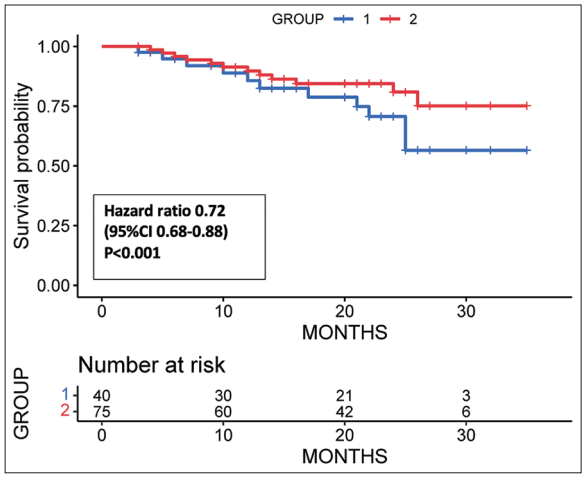

Figure 1: Kaplan–Meier curve showing the overall survival in both the groups

Table 2: The key outcome parameters

Endpoint	ADT alone	ADT + abiraterone	Hazard ratio (95% CI)	*P*
Median time to death	NR	NR	0.72 (0.68–0.88)	-
Median time to PSA progression	8.9 months	21.7 months	0.25 (0.20–0.36)	<0.001
Median time to radograpgic progression	17.4 months	25.4 months	0.40 (0.34–0.68)	<0.001

NR=Not reached, ADT=Androgen-deprivation-therapy, PSA=Prostate-specific antigen, CI=Confidence interval

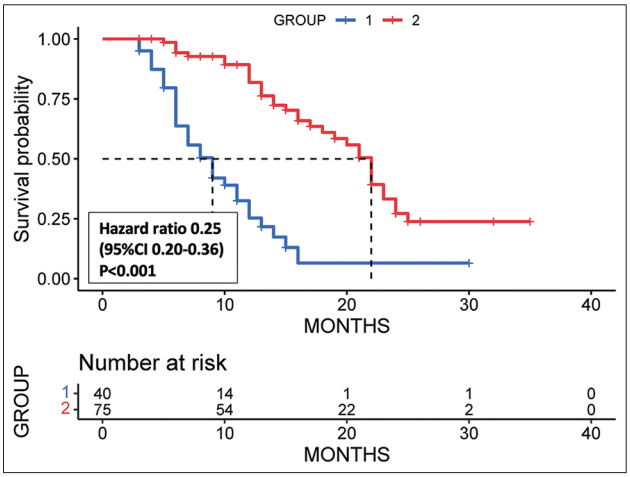

Figure 2: Kaplan–Meier curve showing the prostate-specific antigen progression-free survival in both the groups

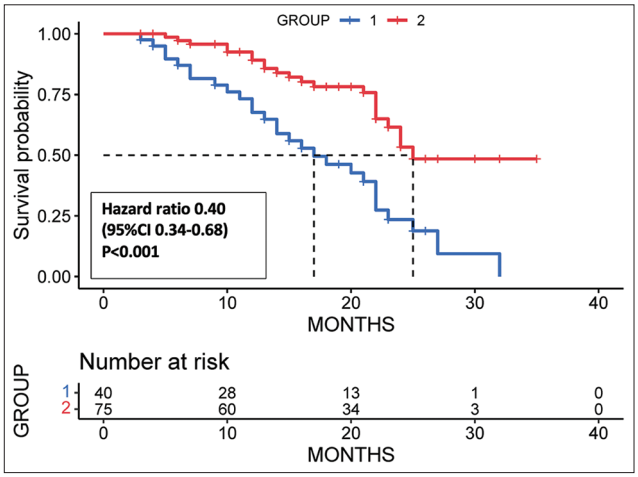

Figure 3: Kaplan–Meier curve showing the radiographic progression-free survival in both the groups

the ADT alone group. One patient in the ADT-only group required dose escalation of insulin after starting treatment. Two patients each in the ADT + abiraterone group and ADT-only group required a change of antihypertensive medication/doses. No patient discontinued treatment due to adverse events.

DISCUSSION

This is the first study on the Indian population, and the results of our study correspond with the trials done on the Western population. However, it is interesting to note that the OS benefit (28% reduction in risk of death in our study vs. 37% and 38% in STAMPEDE and Latitude, respectively) in our study population (both groups) were poorer compared to the corresponding populations in the LATITUDE and STAMPEDE trials.[1,2] Similarly, PSA progression-free survival benefit and the Radiological progression-free survival benefit were also poor compared to STAMPEDE and LATITUDE trial. This finding could be due to a more advanced disease or an aggressive tumor biology in our cohort. Our findings support the use of Abiraterone with ADT as the first-line treatment for newly diagnosed HSPC in Indian men, albeit with a cautionary note that the oncological outcomes might be poorer in Indian population compared to the Western population.

In this observational study, we compared the real-world data of newly diagnosed hormone-sensitive prostate cancer patients treated with ADT alone or ADT + abiraterone at a tertiary care center in the eastern part of India. At a median follow-up of 20.3 months, the median OS could not be calculated in either of the groups since 50% of the patients had not died by that time. However, the 2-year OS was better in group 2 (85% vs. 70%) with a 28% lower risk of death with the addition of abiraterone compared to ADT alone ($P < 0.001$). These results align with the outcomes of two renowned previous trials: The LATITUDE and the STAMPEDE trials. In the LATITUDE trial, a remarkable 38% reduction in the risk of death was observed when abiraterone was added to the treatment regimen compared to ADT alone. Similarly, in the STAMPEDE trial, a 37% reduction in the risk of death was documented in the group that received abiraterone in addition to ADT. These consistent results across multiple studies reinforce the robustness and clinical relevance of the benefits of abiraterone in the treatment of HSPC. Survival data on the Indian population are not available owing to a lack of well-performed studies and results of the studies on the Western population are often extrapolated to our Indian population. A longer follow-up of our cohorts will allow for the OS data to mature.

PSA decline is used to monitor response to treatment. The degree of decline in the PSA levels correlates with the OS outcomes.[5] In our study, the rate of PSA decline >90% compared to baseline was 8.3% higher with the addition of abiraterone to ADT, though not statistically significant. Gupta *et al.* reported that PSA decline >90% was seen in 73.3% with ADT alone compared to 94.4% with ADT + abiraterone ($P = 0.15$).[6] Flaig *et al.* reported that in patients of metastatic HSPC treated with ADT alone and had a suboptimal PSA response at 12 months (PSA >4 ng/ml),

addition of abiraterone resulted in 13% achieving complete response (PSA <0.2 ng/ml) and 33% having partial response (PSA <4 ng/ml).[7] Hussain *et al.* demonstrated that the absolute PSA value after treatment is an independent predictor of survival in a newly detected HSPC.[8] They, also showed that serological complete response (PSA <0.2 ng/ml) was associated with an improved OS. Combined treatment with ADT + abiraterone is shown to achieve higher rates of serological complete response and hence a better OS.

The STAMPEDE, TITAN, ARCHES, and ENZAMET recruited all metastatic patients irrespective of disease volume, whereas the LATITUDE study solely enrolled patients with high-risk disease. Collectively, the data from these studies offer compelling evidence to support the earlier use of newer-generation antiandrogens for patients with mHSPC, including those with low-volume/low-risk disease. Likewise, we have included both low- and high-volume disease in our study.[9]

Other secondary endpoints of radiological progression-free survival and pPFS also strongly support the addition of abiraterone to ADT as the primary treatment. The median pPFS advantage of 12.8 months with abiraterone over ADT alone concurred with that of the LATITUDE trial (25.8 months). The radiological pPFS advantage with abiraterone in our study was 8 months, which is of less magnitude compared to the LATITUDE trial (18.2 months). The significance of these secondary endpoints lies in the early detection of castrate-resistant prostate cancer requiring further line of management options.

Our study is not without limitations. This study was conceived and registered with CTRI for a randomized control trail, but due to the collaborating pharmaceutical company backing out from supplying medications free of cost, it was continued as a prospective observational study. The nonrandomized nature of the study has induced bias. Furthermore, a large number of patients (59%) were lost to follow-up, and this is probably a reflection of real-world data in Indian scenario where patients are lost to follow-up. Furthermore, the duration of follow-up is short to arrive at a meaningful conclusion on the OS. A randomized trial with longer follow-up will throw light on the limitations of this study.

CONCLUSIONS

The addition of abiraterone to ADT in the primary treatment of metastatic HSPC in Indian men results in a significant reduction in the risk of death and the risk of progression (PSA and radiological). This benefit is less in Indian population compared to Western population. Furthermore, the magnitude of the decline of PSA is higher with the addition of abiraterone. A longer follow-up is required for the OS data to mature. A significant number of men discontinue treatment, which reflects the real-world Indian scenario for self-financed treatment options in India.

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