ORIGINAL RESEARCH

A Case Series on the Impact of Abiraterone Acetate with Prednisone in Metastatic Prostate Adenocarcinoma: The Real World Experience

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Objective: To evaluate the clinical benefit of Abiraterone acetate plus prednisone (AA + P) with androgen deprivation therapy in patients with metastatic prostate cancer as a local experience in the Philippines.
Materials and Methods: The authors evaluated retrospectively a case series of seven patients receiving androgen deprivation therapy with high-risk metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC) treated with AA + P in a tertiary hospital from April 2019 to October 2020. Disease characteristics, biochemical trend, quality of life evaluation using the European Organization for Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30 v.3), and adverse events reporting using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 were all retrieved from the medical records as outcome measures.
Results: Analysis of 18 months period using chart review was done. Five patients showed clinical improvement on positive PSA response. Patients also presented with Grade 1-2 adverse events score based on CTCAE including hypertension, hepatotoxicity, gastrointestinal symptoms, and electrolyte imbalances. Using the EORTC QLQ-C30 v.3 showed that AA + P provided significant improvement on the overall quality of life, functioning in terms of role, emotional, cognitive and social aspects with reasonable safety profile and minimal adverse events limited to worsening of gastrointestinal symptoms from baseline.
Conclusion: The addition of AA + P to androgen deprivation therapy is a suitable option for both high-risk mCSPC and mCRPC exhibiting a significant biochemical, functional and quality of life improvement with reasonable safety profile and limited adverse events in the 'real-world' setting, which is comparable with the findings in other similar studies.

Key words: Prostate adenocarcinoma, Abiraterone acetate, prednisone

Introduction

Prostate cancer is the fifth most common cause of cancer related deaths globally accounting for an estimated 366,000 deaths and 6.3 million disability adjusted life years in 2015. It is also the most commonly diagnosed cancer in men, with approximately 1.6 million incident cases in 2015. Although, there have been significant decrease in the mortality of prostate cancer secondary to earlier detection through screening and advancements in the treatment of prostate cancer.[1] Over 3,400 men are diagnosed with prostate cancer every year, with more than 40% of cases localized at the time of

diagnosis and 3% present with metastatic prostate cancer, in which, androgen deprivation therapy is the mainstay of treatment. Castration, either surgical or medical, leads to significant testicular androgen suppression resulting in tumor regression. Despite high initial response rate, nearly all men eventually develop castrate resistant disease.[2] Chemotherapy used to be the only subsequent intervention to improve survival in metastatic disease but has limitations for patients who may not tolerate its toxicity profile and/or not candidates based on co-morbidities. Currently, novel anti-androgens such as Abiraterone acetate have been available as a treatment option in the metastatic castrate resistant prostate cancer either prior to or after Docetaxel.[3] Abiraterone acetate, a potential androgen synthesis blocker, inhibits androgen synthesis from adrenal and intratumoral sources. This potent agent irreversibly inhibits cytochrome P450 17alpha hydroxylase/17.20 lyase (CYP17) thereby blocking androgen synthesis by the adrenal gland, testis as well as within the prostate tumor. It is recommended for chemotherapy naïve patients and after progression on chemotherapy.[2]

Several studies have shown Abiraterone acetate as a well-tolerated, effective alternative to Docetaxel. In the setting of mCRPC, studies have demonstrated a survival benefit over the placebo, prompting further investigation in the hormone naïve population.[3] However, there still exist limited evidence regarding the efficacy and safety in the real-world experience in the Philippine setting. This retrospective case study demonstrates the use of Abiraterone acetate plus prednisone in patients with mCRPC and mCSPC.[2]

Methods

This study was approved and certified by the Armed Forces of the Philippines Health Service Command Research Ethics Committee with protocol number 011/0321. This retrospective case study was conducted at a tertiary military hospital, the Victoriano Luna Medical Center, Quezon City, Philippines in which the authors analyzed the effects of AA + P (Abiraterone acetate 1000 mg daily, given once daily as four 250 mg tablets plus Prednisone 5 mg twice daily) from April 2019 to October 2020 in patients receiving androgen deprivation therapy with high-risk metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC). Chart reviews were done in all of the patients from the initiation of AA + P in a period of 18 months which includes PSA monitoring, global health status or quality of life scores using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) version 3 and patient reported and clinical all-cause adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. All patients signed the informed consent before initiation of AA + P.

Quality of life evaluation along with functional and symptom scores were evaluated using the validated 'tagalog' version of EORTC QLQ-C30 version 3.0 which emphasizes on the patient's capacity to fulfill activities of daily living. Patients instructed to answer upon the initiation of AA + P and at the end of the evaluation. Individual scores and mean scores upon the initiation of AA + P and end of study evaluation were gathered. All of the scales and single-item measures scored from 0-100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status or QoL represents a high QoL, but a high score for a symptom scale represents a high level of symptomatology or problem.[9] A 10-point interval change from baseline tagged as 'improvement' and 'worsening' depending on the scale measured as initially described by Gupta, et al. in 2013.[8]

Results

The patient's characteristics and demographics are presented in Table 1. The median age on this retrospective analysis was 66 years. Of these patients, five (71.4%) presented with Eastern Cooperative Oncology Group (ECOG) performance status of ECOG 0-2 in which one patient with minimal symptomatic bone disease and two (28.6%) presented with performance status of ECOG 3 and 4 in which both presented with symptomatic bone disease. Six patients (85.7%) had bone metastasis, and one patient

(14.3%) had both bone and lymph node metastasis. Two patients (28.6%) presented with grade group 1 to 3 and five patients (71.4%) presented with high grade group of 4 or more. The mean baseline PSA from diagnosis of prostate cancer is 73.1 and 82.6 from the initiation of AA + P.

Table 1. Characteristics of the patients at the start of abiraterone acetate + prednisone treatment.

Characteristics	All (n = 7)	
	N	%
Age		
Median (range)	66 years	(56.0 – 79.0)
Baseline ECOG PS		
0-2	5	71.4
3-5	2	28.6
Symptomatic		
Yes	3	42.6
No	4	57.4
PSA (ng/mL)		
Baseline on diagnosis {mean (range)}	73.1	(9.5 – 169.1)
Baseline prior AA + P {mean (range)}	82.6	(2.82 – 343.0)
Grade Group		
1-3	2	28.6
4-5	5	71.4
High Risk mCSPC	5	71.4
mCRPC	2	28.6
Mean time to CRPC (range)	37 months	(26.0 – 48.0)
Mean testosterone in ng/dL (range)	20.75	(16.3 – 25.2)
Metastasis		
Bones	6	85.7
Nodes	0	-
Bones + Nodes	1	14.3
Duration of AA + P cycles		
Continuous	0	
Interrupted	7	
Mean (range)	4.6 months	(2.0 – 10.0)
Biochemical (PSA) response from initiation of AA + P		
Positive	5	71.4
PSA decrease >50%	3	
PSA decrease <50%	2	
Mean % change (range)	51.6	(11.3 – 90.0)
Negative	2	28.6
Mean % change (range)	34.2	(23.4 – 45.0)

*PSA – Prostate specific antigen; ECOG PS – Eastern Cooperative Oncology Group Performance Status; mCSPC – metastatic castrate-sensitive prostate cancer; mCRPC – metastatic castrate-resistant prostate cancer; AA + P – Abiraterone acetate plus Prednisone

Five patients (71.4%) met at least two of the high-risk prognostic factors (Gleason's score of 8 or more, presence of 3 more lesion on bone scan, or presence of measurable visceral metastasis except lymph node) as initially described in the LATITUDE trial for high-risk metastatic castration-sensitive prostate cancer (mCSPC) and two patients (28.6%) presented with metastatic castration resistant prostate cancer (mCRPC) with mean time to castration-resistance of 37 months with a mean castrate level testosterone of 20.75 ng/dL.

All patients received Abiraterone acetate 1000 mg before breakfast once per day and Prednisone 5 mg twice per day during the duration of investigation but with distinguished variations due to the unavailability of medication for continued intake. The authors analyzed their limited data to assess if AA + P along with androgen deprivation therapy is able to provide clinical benefits in a "real-life" setting in the management of high-risk metastatic castration-sensitive and castration-resistant prostate cancer.

The authors observed that all of the patients considered as interrupted AA + P treatment due to medicine unavailability with an average of 4.6 months treatment duration and ranging from 2 months to 10 months of treatment. Biochemical response to AA + P was measured by utilizing PSA trend and percent PSA change from initiation of treatment. Five (71.4%) patients showed clinical improvement on positive PSA response in which three patients showed more than 50% decrease in PSA levels and two patients had less than 50% decrease in PSA level from the initiation of treatment with a mean % change in PSA of 51.6% which ranged from 11.3% to 90.0%. However, two (28.6%) patients showed no biochemical response during the duration of treatment. In addition, one patient also presented with clinical improvement radiographically based on reduction in the presence of bone metastasis during the investigation as shown in figure 1.

All adverse events were reported using the CTCAE Version 5.0, as shown in Table 2, in which five patients presented with hypertension (grades 1-3), four patients presented with hepatotoxicity (grades 1-2), three patients presented with gastrointestinal symptoms (grade 1-2), and some presented with hypokalemia, hyperglycemia, and peripheral edema. One patient showed urinary incontinence during the study that correlates from his previous surgery. No cardiac disorder, fracture secondary to osteoporosis, nor life-threatening disorders nor death observed.

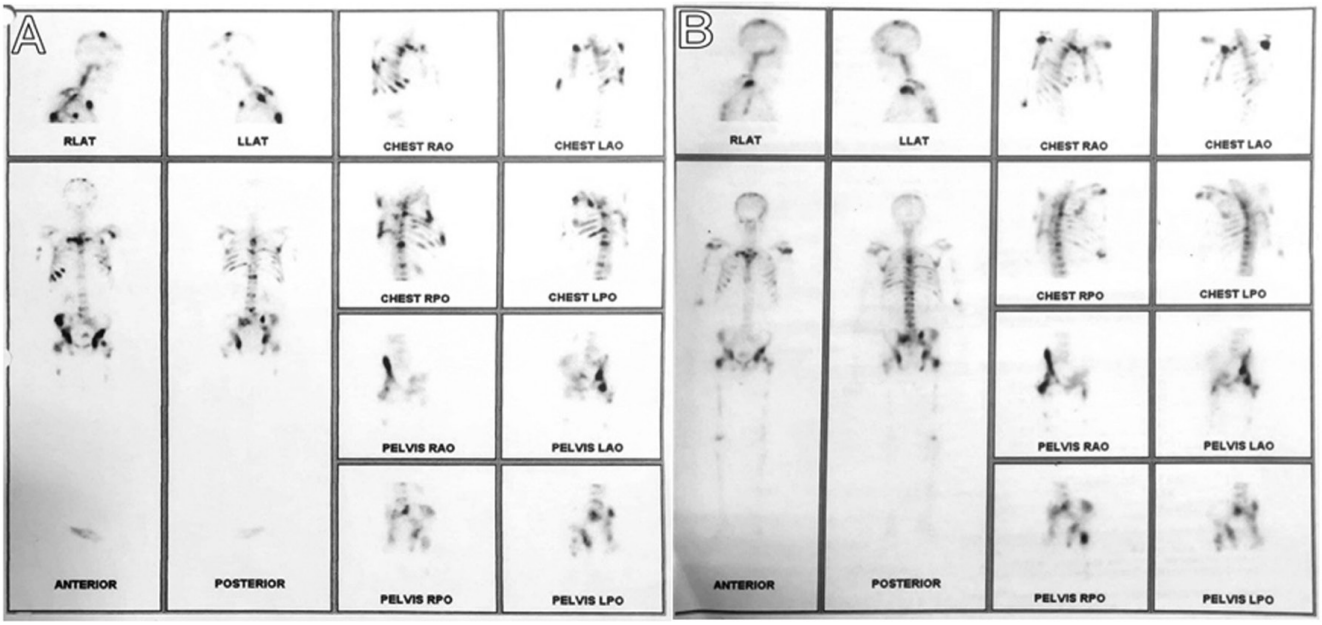

Figure 1. Whole body bone scan of P6 showing regression of bone metastasis during AA + P treatment (A – representing prior AA + P treatment; B – representing during AA + P treatment)

Table 2. Summary of all-cause adverse events of special interest from AA + P measured using CTCAE v5.0

Adverse Events (AE)	All (n = 7).			
	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension	3	1	1	0
Hepatotoxicity				
Increased AST	2	1	0	0
Increased ALT	1	0	0	0
Hypokalemia	1	0	0	0
Hyperglycemia	1	0	0	0
Cardiac Disorders				
Atrial fibrillation	0	0	0	0
Fluid retention or Edema	1	0	0	0
Incontinence	0	1	0	0
GI disturbance				
Nausea	2	0	0	0
Abdominal Pain	0	0	0	0
Diarrhea	1	0	0	0
Constipation	1	1	0	0

Table 3. Patient reported EORTC QLQ-C30 v.3 scores at initiation of AA + P.

Baseline	P1	P2	P3	P4	P5	P6	P7	Mean
QoL Score	83	67	83	75	92	83	75	79
Functional Score	83	54	65	56	78	78	78	70
PF	94	54	60	27	94	67	80	68
RF	100	50	67	100	100	50	78	78
EF	67	53	67	83	53	75	75	68
CF	50	67	67	58	67	83	100	70
SF	67	33	67	50	67	83	83	64
Symptom Score	21	28	21	61	23	17	15	27
FA	33	44	67	100	33	33	11	46
NV	0	0	0	0	0	0	0	0
PA	0	33	50	67	33	0	33	31
DY	0	0	33	0	0	0	0	5
SL	67	33	0	33	33	33	33	28
AP	0	33	0	67	0	0	0	14
CO	67	33	33	100	33	33	0	43
DI	0	0	0	67	0	0	0	10
FI	33	67	33	100	67	67	67	62

*QoL – Quality of Life; PF – Physical functioning; RF – Role functioning; EF – Emotional functioning; CF – Cognitive functioning; SF – Social functioning; FA – Fatigue; NV – Nausea and Vomiting; PA – Pain; DY – Dyspnea; SL – Insomnia; AP – Appetite Loss; CO – Constipation; DI – Diarrhea; FI – Financial Difficulties

Table 4. Patient reported EORTC QLQ-C30 v.3 scores at end of study.

End of Study	P1	P2	P3	P4	P5	P6	P7	Mean
QoL Score	92	100	83	92	83	92	83	89
Functional Score	87	73	76	53	84	94	73	77
PF	100	67	73	20	80	100	73	73
RF	100	67	83	50	83	50	34	67
EF	92	67	67	75	75	100	75	79
CF	83	100	100	100	100	83	100	98
SF	83	83	67	50	83	100	83	78
Symptom Score	18	21	26	69	28	15	30	30
FA	22	22	11	100	33	22	22	33
NV	17	17	33	0	50	0	33	21
PA	0	0	33	83	0	33	33	26
DY	0	0	33	0	0	0	33	9
SL	33	33	0	67	67	0	33	33
AP	0	33	0	67	0	0	0	14
CO	33	33	33	100	33	0	33	38
DI	0	0	33	100	0	0	33	24
FI	67	67	67	100	67	33	67	67

*QoL – Quality of Life; PF – Physical functioning; RF – Role functioning; EF – Emotional functioning; CF – Cognitive functioning; SF – Social functioning; FA – Fatigue; NV – Nausea and Vomiting; PA – Pain; DY – Dyspnea; SL – Insomnia; AP – Appetite Loss; CO – Constipation; DI – Diarrhea; FI – Financial Difficulties

Discussion

Prostate cancer is one the major causes of disease and mortality in men, ranking among the top five cancers for both incidence and mortality. The Global Burden of Disease Cancer Collaboration in 2016, reported it as the most diagnosed cancer in men with approximately 1.6 million incident cases and is the fifth most common cause of cancer-related death globally accounting for approximately 366,000 deaths and 6.3 million disability-adjusted life years last 2015. Prevention of prostate cancer is difficult as it is related with several non-modifiable risk factors such as age, race/ethnicity, family history and genetic variants apart from the modifiable risk factors.[1]

Initially, surgical castration was the only means in achieving androgen deprivation but which followed by biochemical or medical castration via gonadotropin releasing hormone agonists or antagonist, and luteinizing hormone releasing hormone analogues. Androgen deprivation therapy has been the first line of treatment for metastatic prostate cancer until 2015.[3] Despite observed response to ADT, patients usually experience disease progression even though testosterone levels are depressed considered castration resistant disease occurring around 2 to 3 years in majority of its patients. When prostate cancer progresses to more distant sites, prognosis is further affected with a median survival rate of 9 to 30 months.[2,4]

Chemotherapy proved to be a promising intervention in the management of castrate resistant prostate cancer. Docetaxel considered the first line treatment for patients with mCRPC based on the TAX327 and Southwest Oncology Group (SWOG) 9916 trials. These studies showed a survival benefit of around two months for docetaxel plus prednisone compared to then standard of care, minoxantrone.[2,3] More so, chemotherapy was even more successful in the hormone sensitive setting in the CHAARTED, STAMPEDE, and GETUG AFU-15 trials establishing the basis for first line docetaxel chemotherapy alongside ADT in international guidelines for metastatic prostate cancer.[3]

Novel anti-androgen like Abiraterone acetate plus Prednisone has been available as a treatment

option in the mCRPC either prior or after chemotherapy.[5] Abiraterone, irreversibly inhibits CYP17 (17a-hydroxylase/C17,20- lyase), an essential bio-enzyme in androgen biosynthesis that is expressed in testicular, adrenal and prostatic tumor tissues. Abiraterone Acetate 250 mg, to be given in 4 tablets once daily was associated with antitumor effects, including reduced PSA levels and circulating cell tumor counts. It also suppressed serum testosterone levels to undetectable or near undetectable levels after ≤ 28 days of therapy in patients with progressive mCRPC, and in combination with prednisone has suppressed blood and bone marrow aspirate testosterone level to below pg/mL levels in patients with mCRPC, with this suppression maintained at disease progression.[4] The efficacy of AA + P in chemotherapy-naïve mCRPC (COU-AA-302 trial) and post-docetaxel mCRPC (COU-AA-301 trial) was demonstrated in two pivotal, randomized, double blind, global phase 3 trials showing combination therapy with AA + P provided better efficacy than placebo in terms of primary and/or pre-specified secondary outcomes such as overall survival and radiographic progression free survival in chemotherapy naïve patients and overall survival, time to PSA progression, radiographic progression free survival and PSA response in the docetaxel experienced patients.[4]

In patients with metastatic prostate cancer, chemotherapy used to be the only treatment option to improve overall survival and decrease disease progression. In the introduction of novel anti-androgens, such as Abiraterone acetate, showed potential of its efficacy based on recent studies, however in the Philippines, there is absence of studies with the use of AA + P to demonstrate its clinical activity and efficacy on mCRPC and high-risk mCSPC locally in the country due to its luxuriousness.

The LATITUDE study paved way on the initiation of AA + P not only in the treatment of mCRPC but with initiation in patients considered with high-risk mCSPC. It is a multicenter, randomized, double-blind, phase 3 trial which involved 1199 high-risk mCSPC patients divided into two treatment groups (AA + P and placebo treatment arm). It concluded that in a median follow-up of 51.8 months showed that there is significant increase in overall survival of 53.3 months, increased in radiographic progression free survival of 33.0 months, with minimal toxicities such as hypertension and hypokalemia with <1% treatment related deaths.[10]

The authors present the case series grounded within the parameters of the LATITUDE study, showcases the 'real-life' experiences in the local setting. It is limited to a retrospective analysis of seven patients who underwent AA + P treatment in addition to ADT. All of these patients were not given continuous cycles of AA + P due to lack of follow-up during the SARS-COV2 pandemic and unavailability of the medication and was categorized as interrupted regimen with a mean duration of 4.6 months total cycle. They found out that there is a significant biochemical response upon serial PSA measurement on initiation of AA + P. All patients showed >50% PSA reduction in the first 3 months of AA + P use and one patient showed clinical improvement based on the reduction of metastatic bone disease on surveillance whole body bone scan. In addition to PSA reduction, the safety profile of AA + P is also comparable to other studies wherein this series showed that the common adverse events encountered includes hypertension, gastrointestinal symptoms, increased hepatic transaminases, hyperglycemia and hypokalemia. All of the mentioned adverse events prompted observation only without prompt clinical intervention. Using the EORTC QLQ-C30 v.3, they evaluated the quality of life and activities of daily living which showed that AA + P provided clinical improvement on the overall QoL, functioning in terms of role, emotional, cognitive and social aspect with reasonable safety profile and minimal adverse events limited to worsening of gastrointestinal symptoms.

Conclusion

This case series showcases that Abiraterone acetate with prednisone in addition to androgen deprivation therapy. Such combination therapy is a suitable option for both high-risk metastatic castrate-sensitive and metastatic castrate-resistant prostate cancer exhibiting a significant biochemical, functional and quality of life improvement with

reasonable safety profile and limited adverse events in the 'real-world' setting and is comparable with that seen in other similar studies. Nonetheless, these conclusions require further confirmation, preferably in a prospective, randomized clinical trial.

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