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Research Article
First-Line Treatment After the Failure of Androgen Deprivation Therapy for Non-Metastatic, Castration-Resistant Prostate Cancer Men

*Yuhong Zhu, *Gaojie Yang, Yangyang Ding and Lifen Wu

Department of Urology Surgery, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215000, China
*Authors contributed to this research work equally

Abstract

Background and Objective: Abiraterone is recommended by the Chinese guidelines for diagnosis and treatment of prostate cancer 2018 for non-metastatic, castration-resistant prostate cancer men but abiraterone is rarely available in the local market of China and is too expensive. Also, abiraterone has higher≥grade 3 adverse events during the treatment period. Bicalutamide is reported effective and safe for such men. The objectives of the retrospective study were to compare prognostic outcomes, adverse effects and survival of Chinese, non-metastatic, castration-resistant prostate cancer men treated with bicalutamide versus those of men treated with abiraterone. **Materials and Methods:** Database of Chinese men who were diagnosed with non-metastatic, castration-resistant prostate cancer and treated with 50 mg/day bicalutamide (BL cohort, n = 117) or 1 g abiraterone acetate plus 5 mg prednisolone (AB cohort, n = 383) after the failure of androgen deprivation therapy in routine clinical practice were, retrospectively reviewed. **Results:** After 48 months of treatment, prostate-specific antigen doubling time ($p = 0.001$), the prostate-specific antigen response ($p = 0.040$) and metastasis-free survival ($p<0.0001$) were significantly higher among men of the AB cohort than those of the BL cohort. Abiraterone had reported hypertension, impaired liver functions, fracture and pneumonia. Bicalutamide had reported back pain, extremity pain and arthralgia. **Conclusions:** Chinese, non-metastatic, castration-resistant prostate cancer men who received 1 g abiraterone acetate plus 5 mg prednisolone per day had clinical benefits than those who received 50 mg/day bicalutamide but had the risk of adverse effects.

Key words: Abiraterone, bicalutamide, castration-resistant prostate cancer, metastasis, prednisolone, prostate-specific antigen doubling time, prostate-specific antigen response

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Corresponding Author: Lifen Wu, Department of Urology Surgery, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215000, China
Tel/Fax: +86-051267972281

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Androgen deprivation therapy is the main therapeutic option in advanced prostate cancer[1]. Most men show response to androgen deprivation therapy but eventually acquire a phenotype resistant and serum level of prostate-specific antigen level is increased and/or disease progression is reported in radiological analysis, this condition is called castration-resistant prostate cancer[2]. However, prostate cancer men show resistance to androgen deprivation therapy and serum level of prostate-specific antigen level is increased but disease progression is not reported in radiological evaluations like the computed tomography and radionuclide bone scans. This condition is called non-metastatic, castration-resistant prostate cancer[3].

Non-metastatic, castration-resistant prostate cancer is a heterogeneous disease, has the risk of metastasis development, is fatal and has approximately 4 years of survival[4]. Also, a shorter serum level of prostate-specific antigen level doubling time is associated with a shorter time of development of metastasis[3-6]. Apalutamide[7], enzalutamide[8] and abiraterone (second-generation antiandrogen)[9] were found effective to prolong metastasis-free survival and symptoms progression in non-metastatic, castration-resistant prostate cancer men with shorter serum levels of prostate-specific antigen doubling time. Enzalutamide is reported effective than 50 mg bicalutamide (first-generation antiandrogen) in non-metastatic, castration-resistant prostate cancer men[10]. Also, enzalutamide and abiraterone both are recommended by the Chinese guidelines for diagnosis and treatment of prostate cancer 2018 for non-metastatic, castration-resistant prostate cancer men but enzalutamide and abiraterone both are rarely available in the local market of China and are too expensive. Also, abiraterone has higher≥ grade 3 adverse events during the treatment period[11]. Bicalutamide 150 mg therapy is a reported effective and safe treatment approach for non-metastatic, Chinese, castration-resistant prostate cancer men[12]. Therefore, there are controversies regarding the selection of first-line treatment for non-metastatic, Chinese, castration-resistant prostate cancer men.

The objectives of the retrospective study were to compare prognostic outcomes, adverse effects and survival of Chinese, non-metastatic, castration-resistant prostate cancer men treated with bicalutamide versus those of the men treated with abiraterone.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Urology, the First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China from 15 June, 2015-1 October, 2017.

Ethics approval and consent to participate: The design of the study (approval number: HLYJ-Z-202107) was approved by the First Affiliated Hospital of Soochow University review board and the Chinese Society of Oncology. As the study is a retrospective collection of database review, the approval of the study, the registration in the trial registry and informed consent were waived. The study adheres to the law of China and the v2008 Declarations of Helsinki.

Study population: Database of 500 Chinese men who were diagnosed with non-metastatic, castration-resistant prostate cancer and treated with 50 mg/day bicalutamide or 1 g/day abiraterone after the failure of androgen deprivation therapy in routine clinical practice were, retrospectively reviewed (Fig. 1).

Treatments: A total of 117 men were treated with 1 g abiraterone acetate (Zytiga, Janssen-Cilag Ltd., UK) plus 5 mg prednisolone (Wysolone, Wyeth Limited. CA, USA) per day (AB cohort) and 383 men were treated with 50 mg bicalutamide (Casodex, AstraZeneca UK Limited, Luton, LU, UK) per day (BL cohort).

There were no significant differences for clinicopathological parameters (clinical-stage, prostate-specific antigen level, Gleason score, ECOG (The Eastern Cooperative Oncology Group) performance status, treatment history), demographical parameters (age) and the other characteristics between men of both cohorts before the start of treatment ($p>0.05$, Table 1).

Prognostic outcomes

Serum level of prostate-specific antigen doubling time: Serum level of prostate-specific antigen level doubling time at the progression of castration-resistant prostate cancer was evaluated using the log slope method[6].

Serum level of prostate-specific antigen response: Serum level of prostate-specific antigen response was defined as a decline of serum level of prostate-specific antigen level 50% or more from the baseline[13].

Table 1: Clinicopathological parameters, demographical conditions and the other characteristics of men before the start of treatment

	Cohorts		
Treatments	Abiraterone (AB)	Bicalutamide (BL)	Comparisons
Men	117	383	p-value
Clinical stage			
T_2	15 (13)	61 (16)	0.384
T_3	85 (73)	252 (66)	
T_4	17 (14)	70 (18)	
Prostate specific antigen (ng mL^{-1})			
Minimum	4	5	0.105
Maximum	130	130	
Mean±SD	23.52±6.18	24.71±7.15	
Gleason score			
≤7	25 (21)	89 (23)	0.708
>7	92 (79)	294 (77)	
Definitive local therapy			
Prostatectomy	23 (20)	55 (14)	0.859
Radiotherapy	21 (18)	56 (15)	
Androgen deprivation therapy			
Castration	35 (30)	101 (26)	0.477
Combined androgen blockade	82 (70)	282 (74)	
Duration of androgen deprivation therapy (months)			
Minimum	3	4	0.053
Maximum	151	159	
Mean±SD	18.45±5.32	19.68±6.18	
Age (years)			
Minimum	52	50	0.402
Maximum	65	68	
Mean±SD	59.12±9.81	58.25±9.82	
ECOG performance status			
0 or 1	91 (78)	299 (78)	0.999
≥2	26 (22)	84 (22)	
Symptoms			
Symptomatic	12 (10)	31 (8)	0.455
Asymptomatic	105 (90)	352 (92)	
Prostate specific antigen doubling time (months)			
Minimum	7	7	0.059
Maximum	61	62	
Mean±SD	17.51±6.11	18.89±7.15	

ECOG: Eastern cooperative oncology group, constant variables are demonstrated as frequency (percentages) and continuous variables are demonstrated as Mean±Standard deviation (SD), unpaired t-test for continuous variables, chi-square test for independence or Fisher's exact test for constant variables were used for statistical analysis and all results were considered significant if $p<0.05$

Serum level of prostate-specific antigen progression-free survival: The time from the start of bicalutamide or abiraterone treatment to the serum level of prostate-specific antigen progression[13].

Metastasis: Disease progression is reported in radiological evaluations like computed tomography and radionuclide bone scans. Radiological evaluations were performed every 8 weeks.

Survival

Metastasis-free survival: The time from the detection of prostate cancer to the development of metastasis.

Overall survival: The time from the detection of prostate cancer to death.

Adverse events: Events were graded as per National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0[14].

Statistical analysis: InStat 3.01, GraphPad Software, San Diego, CA, USA was used for statistical analysis purposes. The unpaired t-test for continuous variables and Chi-square test for independence or Fisher's exact test for constant variables were used for statistical analysis. All results were considered significant if $p>0.05$.

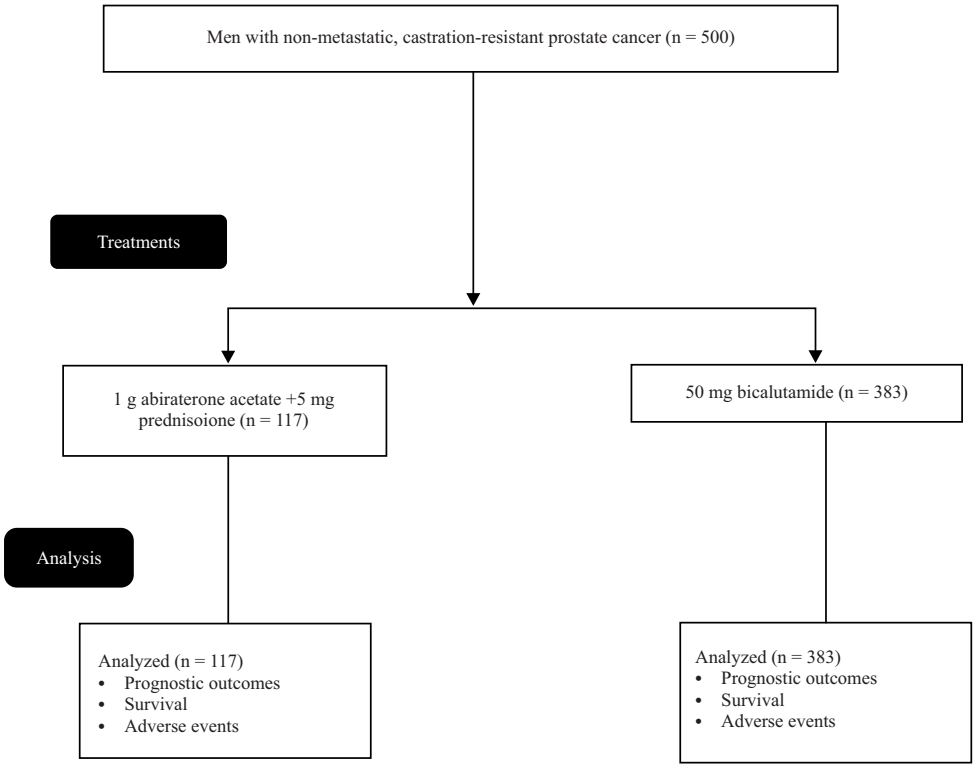

Fig. 1: Flow diagram of the study

RESULTS

Prognostic outcomes and survival: After 48 months of treatment, the prostate-specific antigen doubling time was higher among men of the AB cohort than those of the BL cohort. A total of 80 (68%) men from the AB cohort and 220 (57%) men from the BL cohort have reported prostate-specific antigen response. The prostate-specific antigen response is significantly higher among men of the AB cohort than those of the BL cohort ($p = 0.040$). Prostate-specific antigen progression-free survival was higher among men of the AB cohort than those of the BL cohort. During 48 months 34 (29%) men from the AB cohort and 77 (20%) from the BL cohort have reported metastasis. Metastasis-free survival was higher among men of the AB cohort than those of the BL cohort. A total of 35 (30%) men from the AB cohort and 99 (26%) men from the BL cohort died during 48 months of treatment due to any disease(s) and/or condition(s). Overall survival among men of the AB cohort was the same as those of men of the BL cohort ($p = 0.709$). During 48 months, higher numbers of men from the BL cohort was put on second-line chemotherapies (docetaxel) than those put on second-line chemotherapies of the AB cohort. Higher numbers of men were switched from bicalutamide to abiraterone due to adverse events (hyperglycemia, cataract and arthralgia). The details of outcome measures during 4 years after the start of treatments are reported in Table 2.

Adverse effects: Abiraterone had reported hypertension, increased alanine aminotransferase, increased aspartate aminotransferase, fracture and pneumonia. Bicalutamide had reported back pain, extremity pain and arthralgia. Hyperglycemia and cataract were reported in the men of the AB cohort due to prednisolone. The details of any grade of treatment-emergent adverse events during 4 years are reported in Table 3.

DISCUSSION

The study found that men had higher prostate-specific antigen doubling time, the prostate-specific antigen response and metastasis-free survival if they were treated with 1 g/day abiraterone plus 5 mg/day prednisolone than those of men who were treated with 50 mg/day bicalutamide. The prognostic outcomes of the current study were parallel with those of retrospective studies[13,15,16], the IMAAGEN study[9] and the Terrain trial[10]. Abiraterone acetate plus prednisolone (1 g+5 mg/day) can decrease levels of testosterone and

Table 2: Outcome measures during 4 years after the start of treatment

Outcome measures	Cohorts		
Treatments	Abiraterone (AB)	Bicalutamide (BL)	Comparisons
Men	117	383	p-value
Prostate specific antigen doubling time (months)			
Minimum	7	7	0.001
Maximum	48	48	
Mean±SD	13.55±2.45	12.22±3.51	
Prostate specific antigen response	80 (68)	220 (57)	0.040
Prostate specific antigen progression-free survival (months)			
Minimum	18	14	<0.0001
Maximum	48	48	
Mean±SD	29.31±6.28	25.12±4.59	
Development of metastasis	34 (29)	77 (20)	0.056
Metastasis-free survival (months)			
Minimum	21	18	<0.0001
Maximum	48	48	
Mean±SD	35.12±8.15	29.32±7.31	
Men put on second line chemotherapies	15 (13)	120 (31)	<0.0001
Death due to any cause	35 (30)	99 (26)	0.407
Overall survival (months)			
Minimum	35	31	0.079
Maximum	48	48	
Mean±SD	36.18±8.15	34.22±11.18	
Switch therapy	0 (0)	13 (3)	0.046

Constant variables are demonstrated as frequency (percentages) and continuous variables are demonstrated as Mean±Standard deviation (SD), unpaired t-test for continuous variables, chi-square test for independence or Fisher's exact test for constant variables were used for statistical analysis and all results were considered significant if $p<0.05$

Table 3: Any grade of treatment-emergent adverse events during 4 years after the start of treatment

Any grade of treatment-emergent adverse	Cohorts		
Treatments	Abiraterone (AB)	Bicalutamide (BL)	Comparisons
Men	117	383	p-value
*Hypertension	32 (27)	51 (13)	0.001
Fatigue	27 (23)	81 (21)	0.701
**Back pain	11 (9)	75 (20)	0.011
*Increased alanine aminotransferase	15 (8)	3 (1)	<0.0001
*Increased aspartate aminotransferase	7 (6)	3 (1)	0.002
*Fracture	6 (5)	5 (1)	0.024
**Extremity pain	5 (4)	40 (10)	0.043
*Pneumonia	7 (6)	2 (1)	0.001
Renal failure acute	1 (1)	3 (1)	0.999
Nausea	11 (9)	40 (10)	0.862
Constipation	1 (1)	8 (2)	0.692
Diarrhea	2 (2)	7 (2)	0.999
**Hot flashes	2 (2)	120 (31)	<0.0001
**Arthralgia	2 (2)	82 (21)	<0.0001
***Hyperglycemia	12 (10)	0 (0)	<0.0001
***Cataract	10 (9)	0 (0)	<0.0001

Variables are demonstrated as frequency (percentages), Fisher's exact test was used for statistical analysis and all results were considered significant if $p<0.05$, *Abiraterone-emergent adverse effect, **Bicalutamide-emergent adverse effect and ***Prednisolone-emergent adverse effect

finely prostate-specific antigen[9]. A total of 50 mg bicalutamide per day does not exert the adequate antiandrogen effect[17] and is an insufficient dose for better treatment[18]. Abiraterone delays disease progression of Chinese, non-metastatic, castration-resistant prostate cancer men compared to bicalutamide.

A few numbers of men from the AB cohort were put on second-line chemotherapy compared to those of the BL cohort. The results of second-line chemotherapy of the current study were not parallel with those of a retrospective study[13]. The small sample size of the retrospective study[13] was responsible for contradictory results. A total of 50 mg bicalutamide per day is insufficient to delay prognostic outcomes of Chinese, non-metastatic, castration-resistant prostate cancer men compared to 1 g abiraterone acetate plus 5 mg prednisolone per day.

Any grade of adverse effects especially impaired liver functions was reported higher in amount if men treated with abiraterone compared to bicalutamide. The results of adverse effects of the current study were parallel with those of retrospective studies[13,16], the IMAAGEN study[9] and the Terrain trial[10]. The administration of prednisolone with abiraterone was responsible for higher adverse effects[9]. Not only 50 mg but also 150 mg bicalutamide is well-tolerated by Chinese men[10,18]. A total of 50 mg bicalutamide per day was well tolerated by Chinese, non-metastatic, castration-resistant prostate cancer men compared to 1 g abiraterone acetate plus 5 mg prednisolone per day.

The study found that overall survival time and death of men were not changed with either treatment (abiraterone or bicalutamide). The survival results of the current study were parallel with those of retrospective studies[13,16] but were not parallel with those of a retrospective study[15]. The possible reasons for contradictory results are that patients in a retrospective study[15] were treated with abiraterone acetate or bicalutamide in combination with gonadotropin-releasing hormone antagonist therapy. Any grade of adverse effects was reported higher in amount if men treated with abiraterone plus prednisolone compared to bicalutamide. Also, men had prescribed 5 mg prednisolone/day. However, the United States Food and Drug Administration (USFDA) is approved 10 mg prednisolone/day[9]. This would decrease the survival time of men treated with abiraterone. Abiraterone did not delay the death of Chinese, non-metastatic, castration-resistant prostate cancer men compared to bicalutamide.

Only 13 (3%) patients were switched from bicalutamide to abiraterone and 120 (31%) were switched from bicalutamide to second-line chemotherapies in the conditions were bicalutamide was not found effective. A modest therapeutic efficacy of abiraterone has been reported in castration-resistant prostate cancer patients with anti-androgen withdrawal syndrome after bicalutamide withdrawal[19]. The study suggested second-line chemotherapies in the conditions of failure of first-line bicalutamide in Chinese, non-metastatic, castration-resistant prostate cancer men.

This is a retrospective study, with easily not predictable results. Abiraterone is a very effective drug with more side effects as not shown by other cited studies. The results from this study do bring novelty in the field of urological oncology. However, there are several limitations of the study that have to be reported, for example, retrospective study and lack of randomized trial. the research question would have been better addressed by a study designed and performed as a clinical trial. A possible justification for that patient was on severe conditions that trial would lead to lithal effects. The follow-up period (4 years) is small. Even though 150 mg bicalutamide per day is reported safe, the study population of the BL cohort had received 50 mg bicalutamide per day. The possible justification for the same is that there is no clear instruction for use of 150 mg bicalutamide per day in the Chinese guidelines for diagnosis and treatment of prostate cancer 2018 for non-metastatic, castration-resistant prostate cancer men[11]. Although 10 mg prednisolone/day is approved by USFDA[9]. The study population of the AB cohort had received 5 mg prednisolone/day. The possible justification for the same is that there are high chances of adverse effects if men will have to receive 1 g abiraterone acetate plus 10 mg prednisolone per day[9].

CONCLUSION

Abiraterone increases prostate-specific antigen doubling time, the prostate-specific antigen response and metastasis-free survival of men compared to bicalutamide. A total of 50 mg bicalutamide per day was well tolerated by men compared to 1 g per day abiraterone acetate plus 5 mg per day prednisolone. A total of 1 g/day Abiraterone plus 5 mg/day prednisolone did not delay the death of men compared to 50 mg/day bicalutamide. Because of the unavailability of abiraterone in the local market of China and the high cost of treatment, 50 mg bicalutamide per day could be the competitive treatment for Chinese, non-metastatic, castration-resistant prostate cancer men. The second line chemotherapies are suggested in the conditions of failure of first-line bicalutamide or abiraterone in Chinese, non-metastatic, castration-resistant prostate cancer men.

SIGNIFICANCE STATEMENT

A single-centre, retrospective analysis found that 1 g/day abiraterone plus 5 mg/day prednisolone increases prognostic outcomes of men compared to 50 mg per bicalutamide but had the risk of adverse effects. The study will help urologists

to uncover the critical areas of the treatment strategies for castration-resistant, Chinese, prostate cancer men that many researchers have not evaluated.

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