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ORIGINAL ARTICLE

Comparative assessment of prognostic outcomes between first-generation antiandrogens and novel androgen-receptor-axis-targeted agents in patients with non-metastatic castration-resistant prostate cancer

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Abstract

Background To compare the prognostic outcomes between first-generation antiandrogen (FGA) and novel androgen-receptor-axis-targeted agent (ARATA) as first-line therapy in patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

Methods This study retrospectively included a total of 103 consecutive nmCRPC patients consisting of 47 (45.6%) and 56 (54.4%) who received FGA (bicalutamide or flutamide) and ARATA (abiraterone acetate or enzalutamide), respectively, as the first-line agent after the failure of primary androgen deprivation therapy (ADT).

Results There were no significant differences in the major clinicopathological parameters and previous therapeutic histories between the FGA and ARATA groups. During the observation period, 31 (66.0%) and 29 (51.8%) discontinued first-line therapy in the FGA and ARATA groups, respectively, and of these, 27 (87.1%) and 23 (79.3%) in the FGA and ARATA groups, respectively, were subsequently treated with approved agents as second-line therapy. The prostate-specific antigen (PSA) response rate in the FGA group was significantly lower than that in the ARATA group. Although no significant difference in overall survival was noted between the FGA and ARATA groups, there were significant differences in the PSA progression-free survival on first-line therapy and metastasis-free survival between the two groups, favoring the ARATA group compared with FGA group.

Conclusions Collectively, these findings suggest that among nmCRPC patients who progressed following treatment with the primary ADT, the introduction of ARATA may result in the delay of disease progression compared with FGA.

Keywords Non-metastatic castration-resistant prostate cancer · First-generation antiandrogen · Androgen-receptor-axis-targeted agent · Prognosis

Introduction

Androgen deprivation therapy (ADT) has been regarded as the mainstay for the treatment of patients with advanced prostate cancer (PC) as well as one of the major therapeutic options after the biochemical recurrence in localized PC patients treated with local therapies, including surgery and radiation [1]. The majority of patients with PC initially show a favorable response to ADT; however, nearly all PC patients eventually acquire a phenotype resistant to ADT, termed castration-resistant PC (CRPC), at which point the serum level of prostate-specific antigen (PSA) begins to elevate and/or radiographically detectable disease progression occurs, with a maintained castration level of serum testosterone [2]. If radiological examinations, typically computed tomography (CT) and radionuclide bone scans, reveal negative findings for metastatic disease, this state is recognized as non-metastatic CRPC (nmCRPC) [3].

nmCRPC has been characterized as a heterogeneous disease with respect to the risk of metastatic progression;

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however, once developing metastatic disease, the disease becomes fatal, with a median survival of approximately 3 years [4]. Furthermore, a shorter PSA doubling time (PSADT) is closely associated with a shorter time to metastasis among nmCRPC patients [3–6]. Therefore, delaying the time to metastasis in nmCRPC patients, particularly those with a shorter PSADT, is clinically relevant and may delay the emergence of cancer-associated symptoms and prolong survival in these patients. In recent years, several agents have been demonstrated to prolong metastasis-free survival (MFS) in nmCRPC patients with a shorter PSADT in randomized clinical trials (RCTs) [7–9]. For example, Smith et al. reported that treatment of nmCRPC patients with PSADT ≤ 10 months with apalutamide, a competitive inhibitor of the androgen receptor (AR), significantly improved MFS and time to symptomatic progression compared with a placebo [7].

To date, however, limited information has been available regarding clinical outcomes in patients with nmCRPC treated in routine clinical practice. In Japan, the public health care system supports the use of novel AR-axis-targeted agents (ARATAs), abiraterone acetate and enzalutamide, in nmCRPC patients, and vintage hormonal therapy, such as alternative antiandrogen therapy using first-generation antiandrogens (FGAs), bicalutamide and flutamide, is still widely performed [10]; thus, it may be common to introduce either ARATA or FGA as a first-line agent for nmCRPC patients after the failure of primary ADT. In this study, we retrospectively performed a comparative assessment of prognostic outcomes between FGA and novel ARATA in nmCRPC patients to address the clinical features of these patients treated in real-world clinical practice in Japan.

Patients and methods

Patients

This study was performed by reviewing clinicopathological data from a total of 103 consecutive Japanese patients who were diagnosed with nmCRPC between August 2014 and March 2018, and subsequently treated with either FGA or ARATA as first-line therapy after the failure of primary ADT in a routine clinical setting. In this series, PSA progression against either line of therapy was defined based on the Prostate Cancer Working Group 2 (PCWG2) criteria under the maintenance of a serum testosterone level < 50 ng/dL [11]. In addition, the selection of agents used in either line of therapy was basically conducted based on the preference of the physician without strictly determined criteria. The design of this study was approved by the Research Ethics Committee of our institution, and the need to obtain informed consent for involvement in it from all of the included patients was waived because of its retrospective design.

Treatment

All patients included in this series had been histologically diagnosed with adenocarcinoma of the prostate, and initially received ADT either by castration therapy alone or combined androgen blockade (CAB) consisting of castration plus bicalutamide. When disease progression against primary ADT was observed, the absence of metastasis was confirmed by radiological examinations, including at least chest and abdominal CTs and radionuclide bone scans. Either FGA or ARATA was then introduced as first-line therapy against CRPC. In the FGA group, bicalutamide was introduced in patients previously treated with castration therapy alone, while alternative antiandrogen therapy using flutamide was applied to those receiving CAB [12]. In the ARATA group, either abiraterone acetate (AA) or enzalutamide (Enz) was administered according to the standard dosing schedule reported by Ryan et al. or Beer et al. respectively [13, 14], and dose modification of either agent was permitted considering the degrees of treatment-associated adverse events (AEs) in each patient. In both groups, the treatment introduced after the primary ADT was continued until disease progression or intolerable AEs.

Evaluation

For the objectives of this study, clinicopathological data, including the therapeutic profile, were obtained from the medical records of each patient. Prior to the introduction of either FGA or ARATA, the Eastern Cooperative Oncology Group performance status and serum PSA value were evaluated. Following the start of treatment with either agent, patients were generally evaluated every 6–12 weeks by the assessment of the PSA value in addition to renal, liver and bone marrow functions, while radiological examinations by chest and abdominal CTs and radionuclide bone scans were performed at least every 6 months considering several conditions, such as the symptoms and findings of a blood test, in each patient. The PSA doubling time at CRPC progression was calculated using the log slope method, as previously described [6]. The PSA response was defined as a PSA decline of ≥ 50% from the baseline, while the PSA progression-free survival (PFS) was defined as the time from the initiation of first-line therapy to PSA progression.

Statistical analysis

Statview 5.0 software (Abacus Concepts, Inc., Berkley, CA, USA) was employed in all statistical analyses, and $P < 0.05$ was considered significant. Differences in several parameters

between the two groups were assessed by the unpaired *t* test and Chi square test. OS, PSA PFS and metastasis-free survival (MFS) rates were calculated using the Kaplan–Meier method, and differences were evaluated by the log-rank test.

Results

Table 1 summarizes the characteristics of the 103 nmCRPC patients included in this study. Of these 103, 47 (45.6%) and 56 (54.4%) received FGA and ARATA, respectively, as first-line therapy after the failure of primary ADT, with no significant difference in the major clinicopathological parameters or previous therapeutic histories between the FGA and ARATA groups.

In the FGA and ARATA groups, 17 (36.2%) and 35 (62.5%) patients, respectively, achieved a PSA response, and the PSA response rate in the ARATA group was significantly higher than that in the FGA group (Table 2). Furthermore, PSA PFS in the ARATA group was significantly superior to that in the FGA group (Fig. 1a).

Based on the findings of radiological examinations, 14 (29.8%) and 8 (14.3%) were judged to have developed metastatic diseases in the FGA and ARATA groups, respectively, and there was no significant difference in the proportion of patients with metastatic spread between the two groups (Table 2). However, the MFS in the ARATA group was significantly more favorable compared with that in the FGA group (Fig. 1b).

During the observation period, death from any cause occurred in 7 (14.9%) and 6 (10.7%) patients in the FGA and ARATA groups, respectively, and there was no significant difference in the incidence of overall death between the two groups (Table 2). Additionally, no significant difference in OS was noted between the groups (Fig. 1c).

In the FGA and ARATA groups, 31 (66.0%) and 29 (51.8%), respectively, discontinued first-line therapy due to either disease progression or intolerable AEs. Of these, 27 (87.1%) and 23 (79.3%) in the FGA and ARATA groups, respectively, were subsequently treated with approved agents against CRPC as second-line therapy as follows: AA, Enz and docetaxel for 15 (55.6%), 10 (37.0%) and 2 (7.4%)

Table 1 Characteristics of non-metastatic castration-resistant prostate (nmCRPC) cancer patients who received first-line therapy by first-generation antiandrogen (FGA) or androgen-receptor-axis-targeted agent (ARATA)

	FGA group ($n=47$)	ARATA group ($n=56$)	*P* value
Clinical stage at initial diagnosis (%)			
T2	16 (34.0)	20 (35.7)	0.98
T3	24 (51.1)	28 (50.0)	
T4	7 (14.9)	8 (14.3)	
Mean PSA at initial diagnosis (ng/mL, range)	22.4 (4.4–166.2)	24.3 (5.4–170.7)	0.34
Gleason score[a] (%)			0.87
≤7	9 (19.1)	10 (17.9)	
≥8	38 (80.9)	46 (82.1)	
Definitive local therapy (%)			0.97
Prostatectomy	9 (19.1)	11 (19.6)	
Radiotherapy	6 (12.8)	8 (14.3)	
Type of primary ADT (%)			0.95
Castration	12 (25.5)	14 (25.0)	
Combined androgen blockade	35 (74.5)	42 (75.0)	
Mean duration of primary ADT (months, range)	17.3 (2–174)	16.7 (2–182)	0.16
Mean age at diagnosis of nmCRPC (years, range)	72.9 (52–88)	73.4 (55–86)	0.14
ECOG performance status at diagnosis of nmCRPC (%)			0.63
0 or 1	44 (93.6)	51 (91.1)	
≥2	3 (6.4)	5 (8.9)	
Symptom at diagnosis of nmCRPC (%)			0.44
Negative	44 (93.6)	50 (89.3)	
Positive	3 (6.4)	6 (10.7)	
Mean PSA at diagnosis of nmCRPC (ng/mL, range)	17.4 (2.1–104.2)	16.3 (1.4–122.7)	0.27
Mean PSADT at diagnosis of nmCRPC (months, range)	18.4 (5.1–54.2)	17.2 (6.4–60.7)	0.39

ADT androgen deprivation therapy, *ECOG* Eastern Cooperative Oncology Group, *PSA* prostate-specific antigen, *PSADT* PSA doubling time

[a]Findings on biopsies performed prior to primary ADT

Table 2 Oncological outcomes of first-line therapy by first-generation antiandrogen (FGA) or androgen-receptor-axis-targeted agent (ARATA) and profile of subsequent second-line therapy in non-metastatic castration-resistant prostate cancer patients

	FGA group ($n=47$)	ARATA group ($n=56$)	P value
Prostate-specific antigen (PSA) response (%)	17 (36.2)	35 (62.5)	0.0078
PSA progression-free survival (PFS)			
Median (months)	15.1	Not reached	< 0.001
3-year PSA PFS rate (%)	7.5	59.9	–
Development of metastasis (%)	14 (29.8)	8 (14.3)	0.056
Metastasis-free survival (MFS)			
Median (months)	Not reached	Not reached	0.042
3-year MFS rate (%)	51.1	73.6	–
Death from any cause (%)	7 (14.9)	6 (10.7)	0.52
Overall survival (OS)			
Median (months)	Not reached	Not reached	0.24
3-year OS rate (%)	57.9	75.2	–
Discontinuation of first-line therapy (%)	31 (66.0)	29 (51.8)	0.15
Patients receiving second-line therapy (%)	27 (87.1)	23 (79.3)	0.42
Agents administered as second-line therapy (%)			
Abiraterone acetate	15 (55.6)	2 (8.7)	
Enzalutamide	10 (37.0)	5 (21.7)	
Docetaxel	2 (7.4)	16 (69.6)	

patients, respectively, in the FGA group, and docetaxel, Enz and AA for 16 (69.6%), 5 (21.7%) and 2 (8.7%) patients, respectively, in the ARATA group (Table 2).

Discussion

It has been well documented that nmCRPC has a heterogeneous potential regarding the risk of developing metastatic diseases [4]. In analyses of the placebo groups in RCTs enrolling nmCRPC patients, the median bone MFS (BMFS) is approximately 25 months, whereas nmCRPC patients with unfavorable characteristics, including short PSADT, have a markedly shorter BMFS than other nmCRPC patients [4, 5]. Furthermore, in recently conducted RCTs, two agents, apalutamide and Enz, were shown to significantly prolong PFS and MFS in nmCRPC patients with PSADT ≤ 10 months compared with a placebo [7, 8]. However, it remains unclear whether conventional second-line hormonal therapies, such as FGAs, have effects on the delay of disease progression in nmCRPC patients similar to recently approved agents against high-risk nmCRPC. Considering these findings, this study included a total of 103 consecutive Japanese nmCRPC patients who were treated with either FGA or ARATA as second-line therapy following the failure of primary ADT to retrospectively compare the prognostic outcomes between the FGA and ARATA groups.

Before pivotal RCTs demonstrated the efficacies of apalutamide and Enz for nmCRPC patients [7, 8], observation plus continuous ADT had been regarded as the standard of care for nmCRPC patients, particularly those without short PSADT [3, 4]. Of the 103 nmCRPC patients included in this series, however, 47 (45.6%) and 56 (54.4%) were treated with FGA and ARATA, respectively, after the failure of primary ADT. This different therapeutic strategy for nmCRPC could be explained by the following backgrounds in Japan: so-called vintage hormonal therapies, such as androgen withdrawal and alternative antiandrogen therapy, have been commonly performed even after the introduction of novel ARATAs in routine clinical practice [10], and it is permitted to administer ARATAs to CRPC patients irrespective of the metastatic status by the public health care system. In fact, there were no significant differences in the major clinicopathological parameters or previous therapeutic histories between the FGA and ARATA groups, and approximately 80% of patients in both groups after the discontinuation of first-line therapy either by FGA or ARATA subsequently received approved agents against CRPC. Taken together, we believe that the two groups could be suitable cohorts to comparatively assess the impacts of FGA and ARATA on the prognostic outcomes in nmCRPC patients.

In this series, treatment of nmCRPC patients with ARATA significantly improved prognostic outcomes, including the PSA response rate, PSA PFS and MFS, but not OS, compared with that with FGA. These findings are consistent with those on RCTs enrolling only nmCRPC patients with a short PSADT [7, 8]. Among nmCRPC patients with PSADT ≤ 10 months, Smith et al. reported that the PSA response rate, MFS, PFS, second-PFS and time to symptomatic progression were significantly longer with apalutamide than with placebo [7], while Hussain et al. showed a significantly more favorable PSA

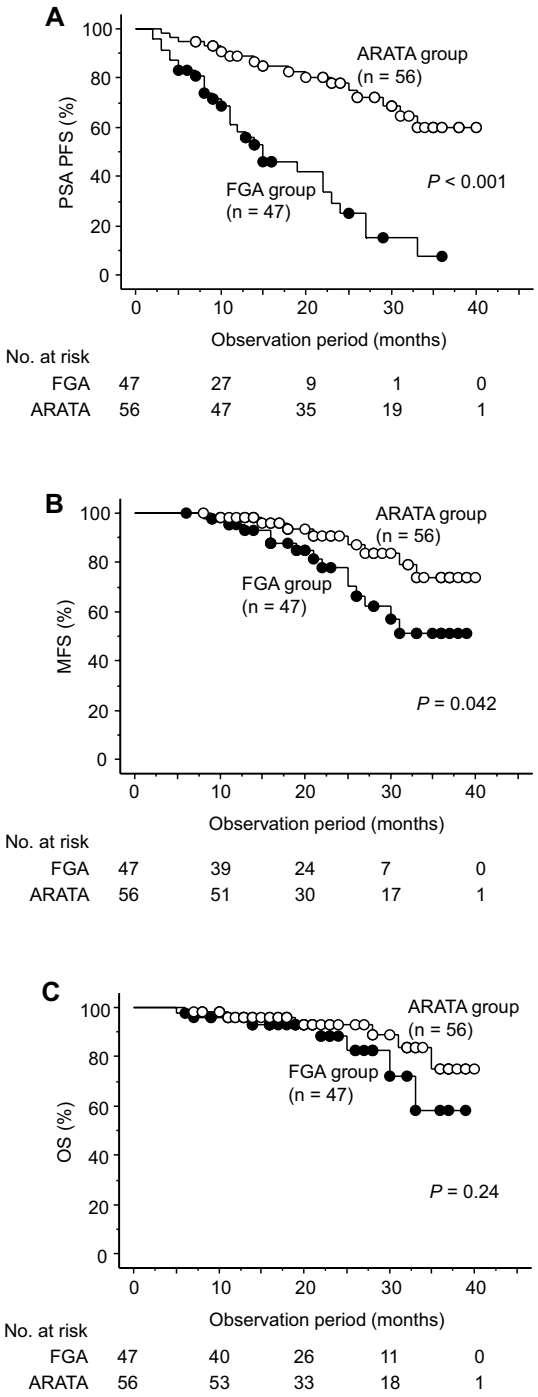

Fig. 1 **a** Prostate-specific antigen progression-free survival (PSA PFS) of 103 non-metastatic castration-resistant prostate cancer (nmCRPC) patients who received either first-generation antiandrogen (FGA) or novel androgen-receptor-axis-targeted agent (ARATA) as first-line therapy after the failure of primary androgen deprivation therapy (ADT). **b** Metastasis-free survival (MFS) of 103 nmCRPC patients who received either FGA or novel ARATA as first-line therapy after the failure of primary ADT. **c** Overall survival (OS) of 103 nmCRPC patients who received either FGA or novel ARATA as first-line therapy after the failure of primary ADT (Censored cases are indicated on the Kaplan–Meier curves as circles)

response rate, MFS, PSA PFS and time to first use of subsequent antineoplastic therapy with Enz than a placebo [8]. In either RCT, however, no significant benefit for the improvement of OS by apalutamide or Enz in these nmCRPC patients was noted compared with the placebo [7, 8]. Furthermore, The STRIVE Trial included CRPC patients who had progressive disease after ADT irrespective of PSADT and randomized them into treatment with either Enz or bicalutamide, and Enz was shown to reduce the risk of disease progression compared with bicalutamide in both nmCRPC and mCRPC patients [15]. These findings strongly suggest the role of novel ARATAs in the delay of disease progression in nmCRPC patients compared with that of FGAs.

Here, we would like to describe several limitations of this study. Firstly, this was a retrospective comparative study with a short observation period including a small number of patients. In fact, the median OS was not reached in the FGA or ARATA group, suggesting that this study may be underpowered to detect a difference in OS between these two groups. Secondly, there was a significant heterogeneity in the therapeutic profiles in both the FGA and ATATA groups. In particular, despite the lack of a significant impact on PSA PSF, MFS or OS (data not shown), the type of primary ADT was not unified in this series. Thirdly, the radiological examinations should be performed under a more intensive schedule to facilitate a definitive finding on MFS. In the two RCTs mentioned above [7, 8], imaging studies were repeated every 16 weeks. In addition, when interpreting the outcomes of this study, it should be considered that novel sensitive imaging modalities, such as prostate-specific membrane antigen positron-emission tomography, may detect metastatic lesions in some patients diagnosed with no evidence of metastases on conventional radiological examinations [16, 17]. Finally, this study targeted all nmCRPC patients without consideration of their risk of metastasis, such as PSADT. Therefore, the application of treatment with ARATAs after the failure of primary ADT may result in overtreatment in some categories of nmCRPC patients; accordingly, it is very important to identify the characteristics of nmCRPC patients showing favorable prognostic outcomes by either continuous ADT alone or in combination with FGA.

In conclusion, the findings based on the retrospective data from Japanese routine clinical practice suggest that despite the lack of a significant difference in the OS between the FGA and ARATA groups, treatment with ARATA could delay the disease progression, including the development of metastases, compared with that with FGA. Therefore, considering the mitigation of cancer-related symptoms and improvement of OS by delaying the progression to metastatic spread as the ultimate goal of treatment for nmCRPC, it might be worthwhile to further investigate the significance of introducing more effective agents, like novel ARATAs

and apalutamide, than FGAs for nmCRPC patients regardless of their risk of metastasis.

Compliance with ethical standards

Conflict of interest All authors have declared no conflict of interest.

References

1. Sharifi N, Gulley JL, Dahut WL (2010) An update on androgen deprivation therapy for prostate cancer. Endocr Relat Cancer 17:R305–R315
2. Fitzpatrick JM, Bellmunt J, Fizazi K et al (2014) Optimal management of metastatic castration-resistant prostate cancer: highlights from a European Expert Consensus Panel. Eur J Cancer 50:1617–1627
3. Rozet F, Roumeguère T, Spahn M et al (2016) Non-metastatic castrate-resistant prostate cancer: a call for improved guidance on clinical management. World J Urol 34:1505–1513
4. Luo J, Beer TM, Graff JN (2016) Treatment of nonmetastatic castration-resistant prostate cancer. Oncology 30:336–344
5. Smith MR, Saad F, Oudard S et al (2013) Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 31:3800–3806
6. Moreira DM, Howard LE, Sourbeer KN et al (2016) Predictors of time to metastasis in castration-resistant prostate cancer. Urology 96:171–176
7. Smith MR, Saad F, Chowdhury S et al (2018) Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 378:1408–1418
8. Hussain M, Fizazi K, Saad F et al (2018) Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 378:2465–2474
9. Ryan CJ, Crawford ED, Shore ND et al (2018) The IMAAGEN study: effect of abiraterone acetate and prednisone on prostate specific antigen and radiographic disease progression in patients with nonmetastatic castration resistant prostate cancer. J Urol 200:344–352
10. Mizokami A, Kadono Y, Kitagawa Y et al (2017) Therapies for castration-resistant prostate cancer in a new era: The indication of vintage hormonal therapy, chemotherapy and the new medicines. Int J Urol 24:566–572
11. Scher HI, Halabi S, Tannock I et al (2008) Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148–1159
12. Momozono H, Miyake H, Tei H et al (2016) Clinical outcomes of anti-androgen withdrawal and subsequent alternative anti-androgen therapy for advanced prostate cancer following failure of initial maximum androgen blockade. Mol Clin Oncol 4:839–844
13. Ryan CJ, Smith MR, Fizazi K et al (2015) Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16:152–160
14. Beer TM, Armstrong AJ, Rathkopf DE et al (2014) Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371:424–433
15. Penson DF, Armstrong AJ, Concepcion R et al (2016) Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE Trial. J Clin Oncol 34:2098–2106
16. Beheshti M, Rezaee A, Geinitz H et al (2016) Evaluation of prostate cancer bone metastases with 18F-NaF and 18F-Fluorocholine PET/CT. J Nucl Med 57(Suppl 3):55S–560S
17. Schwarzenboeck SM, Rauscher I, Bluemel C et al (2017) PSMA Ligands for PET Imaging of Prostate Cancer. J Nucl Med 58:1452–1545