Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naïve castration-resistant prostate cancer: The Kyoto-Baltimore collaboration

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Objectives: To evaluate and compare the efficacy of sequential treatment with abiraterone followed by enzalutamide or vice versa for castration-resistant prostate cancer.

Methods: We retrospectively evaluated data on 198 consecutive chemotherapy-naïve patients who had received both abiraterone and enzalutamide for castration-resistant prostate cancer at Kyoto University Hospital (including satellite hospitals) and at Johns Hopkins Cancer Center. Prostate-specific antigen progression-free survival and overall survival in patients treated with sequential abiraterone-to-enzalutamide versus enzalutamide-to-abiraterone without intervening therapies were compared.

Results: Overall, 113 patients were treated with the abiraterone-to-enzalutamide sequence and 85 with the enzalutamide-to-abiraterone sequence. Median prostate-specific antigen progression-free survival was not significantly different between abiraterone and enzalutamide in the first-line setting (hazard ratio 0.88, 95% confidence interval 0.66–1.19, P = 0.412), but there was an advantage favoring enzalutamide compared with abiraterone in the second-line setting (hazard ratio 0.67, 95% confidence interval 0.49–0.91, P = 0.009). Furthermore, the combined prostate-specific antigen progression-free survival was significantly longer in the abiraterone-to-enzalutamide sequence than in the enzalutamide-to-abiraterone sequence (hazard ratio 0.56, 95% confidence interval 0.41–0.76, P < 0.001). The difference was significant even in multivariate analyses (hazard ratio 0.65, 95% confidence interval 0.42–0.99, P = 0.044). There was no statistical difference in overall survival between the two sequences in univariate (hazard ratio 0.88, 95% confidence interval 0.53–1.43, P = 0.599) and multivariate analyses (hazard ratio 0.81, 95% confidence interval 0.49–1.35, P = 0.427).

Conclusions: The abiraterone-to-enzalutamide sequence might have more favorable efficacy in terms of combined prostate-specific antigen progression-free survival than the enzalutamide-to-abiraterone sequence, although no differences in overall survival were observed. This could possibly be attributable to longer prostate-specific antigen progression-free survival with second-line enzalutamide compared with abiraterone.

Key words: abiraterone, castration resistant, enzalutamide, prostate cancer, sequential therapy.

Introduction

Prostate cancer is the second leading cause of cancer death in the USA,1 and the number of cases are rapidly increasing in Japan as well.2 Patients presenting with advanced disease typically receive hormonal therapy using medical or surgical castration (with or without anti-androgens) as initial treatment. However, most prostate cancer acquires resistance to the initial hormonal therapy over approximately 2–3 years, thus progressing to CRPC.3

Since DTX was introduced in 2004 to prolong the survival of patients with CRPC, there has recently been a rapid increase in the number of effective systemic agents for CRPC, including novel hormonal therapies, immunotherapies, chemotherapies and
radiopharmaceutical drugs. ABI is a CYP17 inhibitor, and ENZA is an anti-androgen targeting multiple steps in the AR signaling pathway. Recently, the metabolites of ABI have been shown to have an antagonistic effect on AR, and are considered to have further potential mechanisms of action.

In the USA, ABI was approved for CRPC in 2012, after showing improved OS in men with metastatic CRPC in the post-DTX and pre-DTX settings, respectively. This was followed quickly by the approval of ENZA, which also showed improved OS both before and after DTX. However, in Japan, ENZA was approved first for use in 2014, several months before ABI was approved. Although their mechanisms are different, the clinical efficacy of these drugs appears very similar. There are no reports yet that directly compare the efficacy of these two agents, although there are several retrospective studies showing the decreased efficacy of the second-line AR-targeting therapy after progression on the first-line therapy. This suggests that there are shared mechanisms of resistance between ABI and ENZA, such as AR-V7 splice variant expression and activating AR mutations, as well as others.

Currently, there is a trend to use these novel hormonal therapies before chemotherapy, because of better tolerability. Elucidating an appropriate treatment sequence of these therapies before chemotherapy, because of better tolerability, is important for maximizing clinical benefit of CRPC patients. Therefore, we carried out a retrospective multi-institutional study in Japan (Kyoto) and the USA (Baltimore) to examine the potential differences in clinical outcomes between the treatment sequences of ABI-to-ENZA and ENZA-to-ABI.

### Methods

The present study was an analysis of consecutive patients who received both ABI and ENZA for CRPC at Kyoto University Hospital including satellite hospitals (Kyoto, Japan) and the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (Baltimore, MD, USA). Only patients that received sequential therapy with ABI-to-ENZA or ENZA-to-ABI (without intervening treatments) were included in this analysis. All patients had pathologically proven adenocarcinoma of the prostate that was progressing according to serum PSA concentrations or radiographic criteria, despite androgen deprivation therapy. This study design was approved by the local institutional review boards of each center. Data were retrospectively obtained from paper and/or electronic medical records. For analysis of clinical outcomes, PSA progression was defined as an increase in PSA values by >25% relative to the baseline or nadir PSA value after ABI or ENZA treatment, as suggested by Prostate Cancer Working Group 2 criteria.

Combined PSA-PFS was measured from the start of the first novel hormonal therapy (ABI or ENZA) until the time of PSA progression on the subsequent (second) AR-directed therapy. OS was defined as the time from initiation of ABI or ENZA treatment to death from any cause.

Descriptive data are presented as medians and ranges. PSA-PFS and OS (i.e. time-to-event outcomes) were estimated using the Kaplan–Meier method, and compared using univariate and multivariate Cox proportional hazard analyses, which were carried out to evaluate the optimal treatment sequence after adjusting for baseline clinical and demographic variables. In multivariate analyses, parameters significantly associated with survival in univariate analysis were included. Baseline characteristics were compared across groups using Fisher’s exact tests and Mann–Whitney tests, as appropriate. All statistical analyses were carried out using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). P-values of <0.05 were considered statistically significant.

### Results

Among 715 patients who had received both ABI and ENZA for CRPC (since 2011 at Johns Hopkins, and since 2014 at Kyoto University), 352 patients received sequential ABI and ENZA (or vice versa) without any intervening therapy: 163 patients received ABI-to-ENZA and 189 patients received ENZA-to-ABI. Baseline patient characteristics had some imbalances between the groups in terms of sequencing preferences (ABI-to-ENZA more common in USA, ENZA-to-ABI more common in Japan) and prior DTX treatment (29% in the ABI-to-ENZA group and 55% in the ENZA-to-ABI group). Therefore, we compared their treatment efficacy only in the DTX-naïve patients, 113 in ABI-to-ENZA group and 85 in ENZA-to-ABI group. Baseline patient characteristics are shown in Table 1, with some imbalances between the groups including number of prior anti-androgen treatment,

#### Table 1 Patient baseline characteristics sequence in chemotherapy-naïve patients according to treatment

<table>
<thead>
<tr>
<th></th>
<th>ABI-to-ENZA sequence (n = 113)</th>
<th>ENZA-to-ABI sequence (n = 85)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyoto University</td>
<td>29 (26%)</td>
<td>71 (84%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>84 (74%)</td>
<td>14 (16%)</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>32 (28%)</td>
<td>20 (24%)</td>
<td>0.518</td>
</tr>
<tr>
<td>8–10</td>
<td>70 (62%)</td>
<td>55 (65%)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>11 (10%)</td>
<td>10 (11%)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>96 (85%)</td>
<td>73 (86%)</td>
<td>0.404</td>
</tr>
<tr>
<td>≥2</td>
<td>6 (53%)</td>
<td>8 (93%)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>11 (10%)</td>
<td>4 (53%)</td>
<td></td>
</tr>
<tr>
<td>Median, range PSA (ng/mL) at start of first agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (19%)</td>
<td>25 (29%)</td>
<td>0.575</td>
</tr>
<tr>
<td>LN</td>
<td>18 (16%)</td>
<td>11 (13%)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>66 (58%)</td>
<td>47 (55%)</td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>8 (7%)</td>
<td>2 (23%)</td>
<td></td>
</tr>
<tr>
<td>No prior anti-androgen‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>68 (60%)</td>
<td>21 (25%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2</td>
<td>45 (40%)</td>
<td>64 (75%)</td>
<td></td>
</tr>
</tbody>
</table>

‡Includes estramustine. NA, not assessed.
such as bicalutamide, flutamide or estramustine (larger in ENZA-to-ABI group than in ABI-to-ENZA group). However, there was no difference in Gleason score, ECOG PS, rate of bone or visceral metastatic disease, or baseline PSA between groups.

PSA response rates were initially evaluated separately in first-line and second-line treatment settings in the ABI-to-ENZA and ENZA-to-ABI groups (Fig. 1). The >50% PSA response rates in the first-line setting were not significantly different in the ABI (48%) and ENZA (55%) groups (Fisher’s exact test, \( P = 0.353 \)). Conversely, the >50% PSA response rates in the second-line setting were significantly better in ENZA (29%) than the ABI (13%) group (Fisher’s exact test, \( P = 0.011 \)), suggesting that ENZA retains clinical activity after ABI, but that ABI is less effective after ENZA.

The PSA-PFS in the ABI-to-ENZA and ENZA-to-ABI groups was first analyzed in unadjusted Kaplan–Meier analysis. We assessed first-line and second-line therapy individually. In the first-line setting, there were no significant differences between ABI and ENZA with respect to PSA-PFS: 194 days (95% CI 137–250) versus 126 days (95% CI 105–165), respectively (HR 0.88, 95% CI 0.66–1.19, \( P = 0.412 \)). In contrast, the median PSA-PFS for second-line ENZA was 91 days (95% CI 67–112), and was significantly longer than 55 days (95% CI 41–69) for second-line ABI (HR 0.67, 95% CI 0.49–0.91, \( P = 0.009 \); Fig. 2). Next, we compared the combined PSA-PFS in these two groups. The median combined PSA-PFS was 455 days (95% CI 385–495) in the ABI-to-ENZA sequence, and was significantly longer than 296 days (95% CI 235–358) in the ENZA-to-ABI sequence (HR 0.56, 95% CI 0.41–0.76, \( P < 0.001 \); Fig. 3a). These results suggest that the longer PSA-PFS durations with ABI-to-ENZA compared with ENZA-to-ABI might partially be explained by the efficacy (or lack thereof) of the second-line AR-directed agent, again implying that ENZA has more efficacy after ABI than vice versa.

With respect to survival, the median OS was 919 days (95% CI 761–not reached) for the ABI-to-ENZA sequence, and 899 days (95% CI 743–not reached) for the ENZA-to-ABI sequence, a difference that was not statistically significant (HR 0.88, 95% CI 0.53–1.43, \( P = 0.599 \); Fig. 3b).

In order to adjust for baseline clinical and demographic factors, variables correlating with PSA-PFS and OS were evaluated by Cox proportional hazards analyses after including treatment sequence (ENZA-to-ABI or ABI-to-ENZA), institution (Kyoto University or Johns Hopkins), Gleason score (<8 or 8–10), ECOG PS (0–1 or >1), baseline PSA (ng/mL), visceral disease (yes or no) and number of prior anti-androgen treatments (0–1 or ≥2). In univariate analysis, the treatment sequence of ABI-to-ENZA (HR 0.56, 95% CI 0.41–0.76, \( P < 0.001 \)), the institution of Johns Hopkins (HR 0.54, 95% CI 0.40–0.74, \( P < 0.001 \)) and higher Gleason score of 8–10 (HR 1.74, 95% CI 1.30–2.34, \( P = 0.002 \)) were significantly correlated with PSA-PFS. In multivariate

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**Fig. 1** Best PSA response rate in each sequence: (a) first-line ENZA, (b) second-line ENZA, (c) first-line ABI and (d) second-line ABI.
analysis including these parameters, the treatment sequence of ABI-to-ENZA (HR 0.65, 95% CI 0.42–0.99, \( P = 0.044 \)) and higher Gleason score of 8–10 (HR 1.77, 95% CI 1.22–2.55, \( P = 0.002 \)) were significant factors correlated with PSA-PFS (Table 2). Baseline PSA levels was significantly correlated with shorter OS in both univariate (HR 1.00, 95% CI 1.00–1.02, \( P < 0.001 \)) and multivariate (HR 1.01, 95% CI 1.00–1.02, \( P = 0.003 \)) analyses. The treatment sequence was not correlated with OS in univariate (HR 0.88, 95% CI 0.53–1.44, \( P = 0.599 \)) and multivariable analysis (HR 0.81, 95% CI 0.49–1.35, \( P = 0.427 \); Table 3).

To elucidate the correlation of treatment efficacy between the sequence, PSA decrease rate and PSA-PFS time were compared between the first- and second-line therapy in each patient. PSA decrease rate and PSA-PFS time was not correlated between the first- and second-line sequence in both ABI-to-ENZA and ENZA-to-ABI groups (Fig. 4). These results showed that the second-line AR-targeting therapy...
might be effective even for the patients for whom first-line therapy was not effective.

**Discussion**

In the present retrospective multi-institutional study of 352 patients with CRPC treated with sequential ABI-to-ENZA or ENZA-to-ABI in Japan and the USA, we compared the PSA response rates, PSA-PFS and OS outcomes in each sequence in chemotherapy-naïve patients. The efficacy of second-line novel hormonal therapy was attenuated after treatment with previous first-line novel hormonal therapy, as previously described. This finding is consistent with previous observations, and might represent a manifestation of cross-resistance between these two novel hormonal therapies.16,17
We previously reported that the PFS tended to be longer in the ABI-to-ENZA sequence than in the ENZA-to-ABI sequence in a preliminary retrospective study of 81 patients (65 receiving ABI-to-ENZA and 16 receiving ENZA-to-ABI) treated at Johns Hopkins; however, the difference was not statistically significant.\(^{18}\) Notably, ABI was approved first in the USA, and it was generally used first instead of ENZA at Johns Hopkins. In contrast, ENZA was approved first in Japan, and it was generally used initially instead of ABI in Kyoto. In the present multi-institutional study, the number of patients increased from 81 to 352, and the number of men receiving each treatment sequence became more well-balanced (163 in ABI-to-ENZA and 189 in ENZA-to-ABI). Here, the difference in PSA-PFS became statistically significant, and continued to favor the ABI-to-ENZA sequence. The higher PSA response rate and the longer PSA-PFS with ENZA versus ABI as the second-line setting provides one plausible explanation for the difference in the combined PSA-PFS observed in the current analysis. However, the difference in the individual PSA-PFS (ABI vs ENZA first-line, ENZA vs ABI second-line) was modest and in fact favored ABI as first-line treatment (median 194 vs 126 days), as well as ENZA as second-line treatment (91 vs 55 days). The combined analysis showed a longer difference of approximately 150 days (455 vs 296 days). The difference in PSA-PFS of the first-line treatment might be caused by the differences in baseline characteristics, especially the number of prior anti-androgen treatments. The bigger difference in the combined analysis factor might be caused by the variable reason for stopping first-line therapy (i.e. PSA, radiographic, symptomatic), with many patients staying on therapy beyond PSA progression.

Why is the clinical efficacy of ENZA potentially better than that of ABI in the second-line CRPC scenario? In a study using a prostate cancer xenograft model, expression levels of AR increased by treatment with ABI in the mouse bearing human prostate cancer tumor cells.\(^{19}\) Importantly, ENZA is known (and was designed) to be effective in CRPC with increased AR expression \textit{in vitro}.\(^{20}\) This might be one of the mechanisms explaining why ENZA was partially effective for ABI-resistant CRPC patients. In contrast, the AR expression of ENZA-resistant prostate cancer cell lines did not increase consistently, showing that non-AR mediated mechanisms are mainly associated with treatment resistance.\(^{21}\)
These mechanisms of resistance to ENZA could not be overcome by ABI. To further elucidate the mechanisms for the cross-resistance between ABI and ENZA, more basic and clinical research will be required, especially in the context of prospective biomarker studies.

In the present study, there was no correlation between the efficacy of first- and second-line therapy. ABI and ENZA target AR in CRPC through different pathways. Even for the primary resistant patients for first-line treatment, second-line treatment might be one treatment option, especially ENZA after ABI (Fig. 4a,c). In ABI after ENZA, three patients showed a PSA decrease of ≥50% and/or PSA-PFS of longer than 200 days after primary resistance to ENZA (Fig. 4b,d). One patient changed treatment because of toxicities, and two patients because of treatment resistance. However, the present study contains only patients who received second-line AR targeting therapy. Therefore, the patients with very aggressive cancer had been excluded, because the physician selected DTX or cabazitaxel after the first-line AR-targeting therapy. It could not be concluded that second-line AR-targeting therapy was indicated for all the CRPC patients.

There were several limitations of the present study. It was a retrospective analysis that included non-randomized treatment allocation, a lack of appropriate controls, an inability to dictate the subsequent treatments in each cohort, a non-standardized time of data collection between patients, difference in the timing of changing ABI-to-ENZA or ENZA-to-ABI in each patient and the inability to appropriately balance the groups with respect to baseline characteristics, especially the number of prior anti-androgen treatments. However, in the multivariate Cox proportional hazard analyses, the treatment sequence significantly correlated with PSA-PFS. Also, treatment efficacy was evaluated only using PSA progression (not by radiological progression), because the timing of radiological assessments after ABI or ENZA treatment was different among patients as a result of divergent institutional and physician/patient preferences. Furthermore, we did not capture data on treatment-related adverse events or dose-reductions/dose-interruptions, so it was not possible to ascertain to what degree side-effects or medication compliance might have influenced the results. Finally, the lack of available biomarker data, such as hemoglobin, alkaline phosphatase or lactate dehydrogenase, from these patients is another significant shortcoming. Therefore, these results require prospective confirmation before they are used to guide clinical practice.

In conclusion, the present study provides preliminary evidence to suggest superiority of the ABI-to-ENZA sequence (compared with ENZA-to-ABI sequence) with respect to PSA-PFS, but not OS in unselected patients with CRPC. Ongoing randomized studies evaluating optimal treatment sequencing will definitely answer this question in the near future.

Acknowledgments

The authors acknowledge the assistance of the following individuals in this study: Takehiko Segawa and Toru Yoshida, Kyoto City Hospital; Keiyu Matsumoto and Hiroshi Okuno, Kyoto Medical Center; Mitsuo Nonomura and Yoshiyuki Okada, Kyoto Katsura Hospital; Jin Yamada and Toru Kanno, Ijinkai Takeda Hospital; Tomoyuki Oida and Norio Kawase, Kosekai Takeda Hospital; Toshiya Aka and Noboru Shibasaki, Otowa Hospital; Keiji Ogura and Satoshi Ishitoya, Otsu Red Cross Hospital; Yasumasa Shichiri and Akihiro Hamada, Otsu Municipal Hospital; Hiroyuki Onishi and Koji Nishizawa, Shiga Medical Center for Adults; Kazuo Nishimura and Kazutoshi Okubo, Osaka Red Cross Hospital; Jun Takenawa, Takatsuki Red Cross Hospital; Hiroshi Kamanaru and Takeshi Soda, Kitanos Hospital; Teruyoshi Aoyama and Kaoru Murakami, Kansai Electric Power Hospital; Mutsushi Kawakita and Takashi Matsuoka, Kobe City Medical Center General Hospital; Noriyuki Ito and Yosuke Shimizu, Nishikobe Medical Center; Yoji Taki, Jun Watanabe, Toyoka Public Hospital; Hiroshi Iwamura and Ayumu Matsuuda, Hmeji Medical Center; Kazuhiro Okumura and Hiroaki Kawaniishi, Tenri Hospital, and Tadashi Hayashi and Masa-hiro Tamaki, Japanese Red Cross Society Wakayama Medical Center.

Conflict of interest

ESA has served as a paid consultant/advisor to Janssen, Johnson & Johnson, Medivation and Astellas; he has also received research funding to his institution from Janssen, Johnson & Johnson, Medivation and Astellas. The other authors declare no conflict of interest.

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Editorial Comment

Editorial Comment to Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naïve castration-resistant prostate cancer: The Kyoto-Baltimore collaboration

Which should come first for treatment of chemotherapy-naïve castration-resistant prostate cancer (CRPC), abiraterone (ABI) or enzalutamide (ENZA)? This question is one of the major concerns in considering a treatment strategy for CRPC. Terada et al. showed that ABI-to-ENZA is superior to ENZA-to-ABI, which answered the question to some extent, but this study has several important limitations that should be understood with caution. First, this study was retrospective, and baseline characteristics between the USA and Japan were largely different. The use of flutamide or estramuscine might be significantly lower in the USA than in Japan, which means response to ABI or ENZA might be better in USA patients than Japanese patients. Furthermore, there is a large difference in terms of sequencing preferences (ABI-to-ENZA more common in the USA, ENZA-to-ABI more common in Japan), which should have influenced the results of this study. Second, the mechanisms of differences in the second-line efficacy of ABI and ENZA have not been fully investigated, as the author described in the Discussion. Third, the benefit of sequential use of these androgen receptor axis-targeted agents on overall survival was not shown. The trend of CRPC treatment has been moving to the use of chemotherapy after failure of first-line ENZA or ABI. In contrast, recent similar studies also showed superiority of ABI-to-ENZA to ENZA-to-ABI. Maughan et al. carried out a retrospective analysis of 81 consecutive metastatic CRPC patients at Johns Hopkins including 65 patients treated with ABI-to-ENZA and 16 patients treated with ENZA-to-ABI. In the multivariate analysis, the ABI-to-ENZA group showed a better progression-free survival compared with the ENZA-to-ABI group (hazard ratio 0.37, 95% CI 0.22–0.64, P < 0.001). Miyake et al. also carried out a retrospective analysis in 108 consecutive patients with metastatic CRPC who sequentially received ABI and ENZA, including 49 patients with ABI-to-ENZA and the others with ENZA-to-ABI. The combined prostate-specific antigen progression-free survival in the ABI-to-ENZA group (median 18.4 months) was significantly superior to that of the ENZA-to-ABI group (median 12.8 months). These studies including this study were all retrospective and showed no significant difference in overall survival, but might affect our treatment strategy in patients with chemotherapy-naïve CRPC. Ongoing prospective randomized trials or future studies should be expected to resolve the above problems.

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DOI: 10.1111/iju.13379

Conflict of interest
None declared.

References
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