Useful predictors of progression-free survival for Japanese patients with LATITUDE-high-risk metastatic castration-sensitive prostate cancer who received upfront abiraterone acetate

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Objective: Recently, hormonal therapy using abiraterone acetate, a second-generation androgen receptor axis-targeted agent, was reported to improve overall survival and progression-free survival in men with LATITUDE-high-risk metastatic castration-sensitive prostate cancer. This observational multicenter study aimed to assess the efficacy of upfront abiraterone acetate in Japanese patients with LATITUDE-high-risk metastatic castration-sensitive prostate cancer.

Methods: The present study included 112 Japanese patients with LATITUDE-high-risk metastatic castration-sensitive prostate cancer who received upfront abiraterone acetate at four institutions belonging to the Tokai Urologic Oncology Research Seminar group, between January 2018 and September 2020. Progression-free survival and overall survival were assessed, and Cox regression analyses were carried out to evaluate the prognostic significance of upfront abiraterone acetate for progression-free survival.

Results: Within a median follow-up period of 13 months, the progression-free survival and overall survival rates were 76.8% and 89.3%, respectively. Both univariate and multivariable Cox regression analyses showed that the presence of Gleason pattern 5, performance status and hemoglobin were independent predictors of progression-free survival. The patients were subsequently divided into three groups as follows: group 1, 17 patients negative for these three independent progression-free survival predictors; group 2, 49 patients with one positive independent progression-free survival predictor; and group 3, 45 patients with two or three independent progression-free survival predictors. Progression-free survival was significantly different among these three groups (P < 0.001).

Conclusion: Upfront abiraterone acetate might provide satisfactory outcomes for Japanese patients with LATITUDE-high-risk metastatic castration-sensitive prostate cancer. Gleason pattern 5, performance status and hemoglobin are potential predictors of progression-free survival in Japanese patients with LATITUDE-high-risk metastatic castration-sensitive prostate cancer who received upfront abiraterone acetate.

Key words: abiraterone acetate, LATITUDE-high-risk, metastatic castration-resistant prostate cancer.

Background

Most mCSPC patients have an initial response to ADT. However, the majority of these patients progress to CRPC within a median of approximately 1 year. ADT plus docetaxel has been widely accepted as one of the standard treatments for patients with mCSPC who are eligible for chemotherapy, especially those with a high metastatic burden. Recently, second-generation ARAT agents were added to ADT, including Abi, Enz or Apa. These have been shown to significantly benefit patients with mCSPC compared with ADT monotherapy. Among them, hormonal therapy using Abi, which is the prodrug of abiraterone and inhibits cytochrome P-450c17, a critical enzyme in androgen biosynthesis, was reported to improve OS and radiographic PFS in men with high-risk mCSPC who show...
at least two of the following factors: (i) Gleason score ≥8; (ii) at least three bone lesions; and (iii) the presence of visceral metastasis (LATITUDE criteria). Enz with ADT significantly reduced the risk of metastatic progression or death overtime versus placebo plus ADT in men with mCSPC, including those with low-volume disease and/or prior docetaxel. In the TITAN clinical trials of Apa, OS and radiographic PFS were significantly longer when Apa was added to ADT than that with placebo plus ADT. Furthermore, the side-effect profile did not differ substantially between the two groups. However, as these recent introductions of upfront ARAT agents could produce certain benefits for mCSPC patients, current therapeutic strategies for them have become markedly complex, occasionally resulting in difficulties in decision-making in real-world clinical practice.

Considering these findings, it is necessary to understand the prognostic factors of upfront ARAT agents for patients with mCSPC. Therefore, in the current study, we focused on upfront Abi use in LATITUDE-high-risk Japanese mCSPC patients. We retrospectively analyzed the prognostic outcomes of Japanese patients with LATITUDE-high-risk mCSPC who received upfront Abi and developed a novel system to stratify the prognosis of these patients.

**Methods**

In the current study, we retrospectively analyzed the clinical data of 112 Japanese patients with LATITUDE-high-risk mCSPC who received upfront Abi between January 2018 and September 2020 at four institutions belonging to the Tokai Urologic Oncology Research Seminar group, including the Fujita Health University School of Medicine, Nagoya City University Graduate School of Medical Sciences, Hamamatsu University School of Medicine and Gifu University. The design of this study was approved by the ethics committee of these four institutions (approval no: HM20-465, 60-21-0018, 2021-042, 21-051). The requirement for informed consent from all patients included in this study was waived because of the retrospective design.

In the present study, all the patients fulfilled the LATITUDE criteria, which means patients had at least two of the following factors: (i) Gleason score ≥8; (ii) at least three bone lesions; (iii) and the presence of visceral metastasis. The patients received ADT combined with oral Abi (1000 mg once daily) + prednisolone (5 mg or 10 mg once daily). Baseline assessments were carried out before the introduction of Abi. The Gleason score was obtained from the prostate biopsy. PS was assessed using the ECOG–PS, and laboratory data including initial PSA, Hb and ALP were measured using standard methods. Patients also underwent radiological examinations, including pelvic magnetic resonance imaging, computed tomography and radionuclide bone scanning, to determine the cTNM stage. Clinical, biochemical or radiographic progressive disease was defined according to the criteria of the Prostate Cancer Clinical Trials Working Group 3.

All data were analyzed using IBM spss Statistics version 23 (SPSS Japan, Tokyo, Japan). A P-value of <0.05 was considered significant. OS and PFS were estimated using the Kaplan–Meier method, and differences were determined using the log-rank test. Univariate and multivariable analyses were carried out using Cox proportional hazards regression.

**Results**

The clinical characteristics of the 112 Japanese patients with LATITUDE-high-risk mCSPC who received upfront Abi included in the present study are summarized in Table 1.

During the observation period with a median follow-up period of 13 months, the OS and PFS rates were 89.3% and 76.8%, respectively (Fig. 1).

All AEs appeared in 32 patients (28.6%). Detailed information about the AEs is shown in Table S1.

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**Table 1 Baseline patient characteristics**

| Variables                  | n = 112 |
|----------------------------|---------|
| Median age, years [IQR]    | 74 (68–79) |
| Median initial PSA, ng/mL [IQR] | 291.9 (77.9–1265.0) |
| Gleason score (%)          |         |
| 4 + 3                      | 1 (0.9) |
| 4 + 4                      | 38 (33.9) |
| 5 + 3                      | 1 (0.9) |
| 4 + 5                      | 37 (33) |
| 5 + 4                      | 21 (18.8) |
| 5 + 5                      | 13 (11.6) |
| Unknown                    | 1 (0.9) |
| cT (%)                     |         |
| 2a                         | 4 (3.6) |
| 2b                         | 3 (2.7) |
| 2c                         | 13 (11.6) |
| 3a                         | 26 (23.2) |
| 3b                         | 31 (27.7) |
| 4                          | 35 (31.3) |
| cN (%)                     |         |
| 0                          | 50 (44.6) |
| 1                          | 62 (55.4) |
| No. bone metastasis, n (%) |         |
| 0                          | 7 (6.3) |
| 1 or 2                     | 5 (4.5) |
| ≥3                         | 100 (89.3) |
| Use of bone-modifying agents, n (%) | 70 (62.5) |
| Visceral metastasis, n (%) |         |
| None                       | 71 (63.4) |
| Lung                       | 36 (32.1) |
| Liver                      | 2 (1.8) |
| Others                     | 3 (2.7) |
| ECOG PS, n (%)             |         |
| 0                          | 86 (76.8) |
| 1                          | 12 (10.7) |
| 2                          | 12 (10.7) |
| 3                          | 2 (1.8) |
| HB, g/dL, median [IQR]     | 13.4 (11.7–14.5) |
| ALP, IU/mL, median [IQR]   | 450.5 (262–1148) |
| Local radiation therapy, n (%) | 2 (1.8) |
| Subsequent therapy, n (%)  |         |
| None                       | 82 (73.2) |
| Enzalutamide               | 12 (10.7) |
| Bicalutamide               | 3 (2.7) |
| Flutamide                  | 1 (0.9) |
| Docetaxel                  | 8 (7.1) |
| Others                     | 6 (5.4) |
To investigate the important factors affecting PFS in Japanese patients with LATITUDE-high-risk mCSPC who received upfront Abi, Cox regression analysis was carried out. In the univariate analysis, Gleason pattern 5, PS and Hb were identified as important predictors of PFS ($P = 0.033, 0.004$ and $0.006$, respectively). Multivariable analysis using these three important predictors showed that all of these factors were independently associated with PFS (Gleason pattern 5: HR $0.235$, 95% CI $0.077$–$0.714$, $P = 0.011$; PS: HR $0.223$, 95% CI $0.098$–$0.506$, $P = 0.000$; Hb: HR $0.269$, 95% CI $0.113$–$0.644$, $P = 0.003$, respectively; Table 2).

Regarding the Gleason pattern 5, PS and Hb, Kaplan–Meier curves of PFS are shown in Fig. 2. In each category, a significant difference in PFS was observed (Gleason pattern 5, PS and Hb; $P = 0.023, 0.002$ and $0.003$, respectively).

Considering the three independent predictors of PFS, we stratified the 111 patients into three groups as follows: group 1, 17 patients negative for these three independent PFS predictors; group 2, 49 patients with one positive independent PFS predictor; and group 3, 45 patients with two or three independent PFS predictors. The PFS was significantly different among the three groups ($P < 0.001$; 0 factor vs 1 factor: $P = 0.1465$; 0 factor vs 2 or 3 factors: $P = 0.0028$; 1 factor vs 2 or 3 factors: $P = 0.0008$, respectively; Fig. 3).

**Discussion**

According to the extent of metastatic disease and presence of symptoms, the estimated mean survival of mCRPC patients was 9–36 months. Despite recent introductions, such as ARAT, docetaxel or cabazitaxel, the prognosis of these patients after the mCRPC stage has not dramatically improved. Accordingly, it is necessary to provide optimal treatment for the mCSPC stage and delay the mCRPC stage for as long as possible.

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**Table 2** Univariate and multivariable analyses of the clinical parameters of PFS

| Predictor                                | Univariate analysis | Multivariable analysis |
|------------------------------------------|---------------------|------------------------|
|                                          | HR (95% CI)         | $P$-value              | HR (95% CI) | $P$-value |
| Age ($\geq 74$ vs $<74$ years)           | 0.525 (0.233–1.183) | 0.120                  |            |          |
| Initial PSA ($\geq 291.9$ vs $<291.9$ ng/mL) | 1.708 (0.772–3.778) | 0.186                  |            |          |
| Existence of Gleason pattern 5 (yes vs no) | 0.312 (0.107–0.909) | 0.033                  | 0.235 (0.077–0.714) | 0.011    |
| Clinical stage cT2                       |                     |                        |            |          |
| cT3                                      | 1.214 (0.396–3.714) | 0.735                  |            |          |
| cT4                                      | 1.022 (0.423–2.467) | 0.962                  |            |          |
| cN (+ vs –)                              | 0.663 (0.295–1.489) | 0.319                  |            |          |
| No. bone metastasis                      |                     |                        |            |          |
| 0                                        |                      |                        |            |          |
| 1 or 2                                   | 2.365 (0.814–6.869) | 0.114                  |            |          |
| $\geq 3$                                 |                      |                        |            |          |
| Visceral metastasis none                 |                      |                        |            |          |
| Lung                                     | 0.695 (0.092–5.261) | 0.724                  |            |          |
| Liver                                    | 0.566 (0.070–4.556) | 0.592                  |            |          |
| Others                                   | 0.891 (0.055–14.453) | 0.935                  |            |          |
| ECOG PS ($\geq 1$ vs 0)                  | 0.313 (0.143–0.683) | 0.004                  | 0.223 (0.098–0.506) | 0.000    |
| Hb ($\geq 13.1$ [n = 50] vs $\geq 13.1$ [n = 62] g/dL) | 0.293 (0.123–0.698) | 0.006                  | 0.269 (0.113–0.644) | 0.003    |
| ALP ($\geq 350$ [n = 66] vs $<350$ [n = 46] IU/mL) | 0.491 (0.206–1.170) | 0.108                  |            |          |
| Local radiation therapy (yes vs no)      | 20.752 (0.000–5639103) | 0.635                  |            |          |
possible. Several recent investigators have advocated the time from diagnosis to CRPC as a significant prognosticator of OS.\textsuperscript{15–17} Regarding the treatment of mCSPC patients, according to the network meta-analysis, ADT plus Abi or Apa might provide the largest OS benefits, with relatively low serious AE risks. Enz might improve radiographic PFS to the greatest extent, but a longer follow up is required to examine the OS benefits associated with Enz.\textsuperscript{18} Recently, Harada \textit{et al.} showed a possible treatment strategy for patients with mCSPC as per cancer and patient characteristics, as well as patient preference.\textsuperscript{19} However, to date, the prognostic factors of upfront ARAT agents for Japanese patients with mCSPC have not been widely introduced into real-world clinical practice. Collectively, further prognostication should be carried out to provide more precise information regarding the treatment of Japanese patients with mCSPC. For the mCSPC stage, current decision-making in real-world clinical practice should focus on Abi, which is an ARAT agent for upfront use in LATITUDE-high-risk Japanese mCSPC patients.

In the current study, we retrospectively analyzed the data of 112 Japanese patients with LATITUDE-high-risk mCSPC who received upfront Abi. Both univariate and multivariable Cox regression analyses showed that the presence of the Gleason pattern 5, PS and Hb were independent predictors of PFS. Regarding the Gleason pattern 5, prostate cancer with a Gleason score 9–10 is indicative of particularly aggressive disease.\textsuperscript{20–22} PS as a prognostic factor for OS has been evaluated in men with CRPC.\textsuperscript{23} Furthermore, several recent investigators have advocated that anemia is a powerful prognostic factor in PC.\textsuperscript{24,25} In particular, Okamoto \textit{et al.} reported that pretreatment anemia was an independent prognostic factor that predicted oncological outcomes among mCSPC patients treated with ADT monotherapy or complete androgen blockade.\textsuperscript{25} Regarding the prognostic factor of upfront Abi used for LATITUDE-high-risk mCSPC patients, a recent study reported pretreatment anemia was a prognostic factor among mCSPC patients who received upfront Abi.\textsuperscript{26}

To properly predict the clinical outcomes of Japanese mCSPC patients who receive upfront Abi, we attempted to develop a novel system for the prognostic stratification of these patients by using three independent PFS predictors, the Gleason pattern 5, PS and Hb. We divided the patients into three groups based on the presence of none, one and two or three independent PFS predictors. We then compared PFS among the three groups. The results of the present study supported our novel stratification system, suggesting that the positive numbers of independent PFS predictors could be a useful tool for the treatment of Japanese patients with LATITUDE-high-risk mCSPC who receive upfront Abi.

The present study had several limitations. First, this was a retrospective study with a small sample size and a short-term follow-up period. In particular, because of the short observation period with a median follow-up period of 13 months, proper analyses assessing prognostic factors for OS could not be carried out considering the high OS rates. Second, the cut-off points used in the current analyses should be assessed in a large-scale study. Third, we could not obtain sufficient patient information, including their comorbidities, past history and the extent of disease of bone metastasis. Future prospective studies with much larger sample sizes and longer follow-up periods are required to confirm the findings of the current study.

In conclusion, we identified that upfront Abi might provide satisfactory clinical outcomes for Japanese patients with LATITUDE-high-risk mCSPC. The Gleason pattern 5, PS
and Hb levels might be considered as useful predictors of PFS in these patients. Furthermore, our novel stratification system based on the positive numbers of these three independent PFS predictors could help guide decision-making for the treatment of Japanese patients with LATITUDE-high-risk mCSPC who receive upfront Abi.

**Conflict of interest**

None declared.

**Approval of the research protocol by an Institutional Reviewer Board**

The design of this study was approved by the ethics committee of the four institutions (approval no: HM20-465 [Fujita Health University School of Medicine], 60-21-0018 [Nagoya City University Graduate School of Medical Sciences], 2021-042 [Hamamatsu University School of Medicine], 21-051 [Gifu University]).

**Informed consent**

Not applicable.

**Registry and the Registration No. of the study/trial**

Not applicable.

**Animal studies**

Not applicable.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1. Adverse events.