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Current Status of Sequential Treatment for Castration-resistant Prostate Cancer: A Retrospective Analysis

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Abstract. *Background/Aim: Although multiple treatments are available for metastatic castration-resistant prostate cancer, data to determine the optimal treatment sequence are limited. This study aimed to investigate the current status of drug therapy for castration-resistant prostate cancer and clarify the sequential treatment in actual clinical practice. Patients and Methods: This retrospective study included 425 patients diagnosed with castration-resistant prostate cancer at Showa University Hospital and affiliated hospitals between January 2014 and December 2021, who were treated with any of the following four drugs: novel androgen receptor signal inhibitors (abiraterone acetate and enzalutamide) and anticancer drugs (docetaxel and cabazitaxel). We investigated the actual treatment choices for castration-resistant prostate cancer, focusing on the order of administration of the four drugs. This analysis was visualized using a Sankey diagram. Results: Regarding the number of drugs administered, most patients received one type of drug, with androgen receptor signal inhibitors being the most commonly administered (total, 179; enzalutamide, 139 and abiraterone acetate, 40). Enzalutamide was the most frequently selected first-line drug (58.4%). The most common sequence for second-line treatment was androgen receptor signal inhibitor-androgen receptor signal inhibitor (n=96), followed by androgen receptor signal inhibitor-docetaxel (n=85), docetaxel-androgen receptor signal inhibitor (n=59), and docetaxel-cabazitaxel (n=6). Conclusion: Androgen receptor signal inhibitors is the most commonly used drug category for first-line treatment of castration-resistant prostate cancer, with enzalutamide being the most commonly used drug. Further investigations are required regarding patient background and prognosis.*

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In general urological practice in Japan, hormone therapy is often used to treat prostate cancer when curative treatment is unsuitable due to the patient's advanced age or other reasons. In Japan, the proportion of combined androgen blockade (CAB) as a first-line hormone therapy for prostate cancer is higher than that in Europe and the United States, and CAB has been used in clinical practice for a long time. Given the increase in the average life expectancy of men and prevalence of hormone therapy in Japan, the number of patients with castration-resistant prostate cancer (CRPC) is expected to increase. There are multiple treatments for metastatic CRPC (mCRPC), but data on the optimal treatment sequence are limited. To guide the selection and sequence of treatment, individual treatment strategies must be considered along with patient preferences and factors, such as age, comorbidities, drug tolerability, and economic situation. Prostate cancer in Japan is on the rise, and it ranks the first among males. Androgen deprivation therapy (ADT) is the standard treatment for metastatic cancer; however, the American Urological Association and National Comprehensive Cancer Network guidelines do not include ADT as a standard initial treatment for localized prostate cancer. However, in cases where radical treatment is not appropriate owing to advanced patient age, hormone therapy is frequently

used as a treatment for prostate cancer in general urological clinical practice in Japan. Cancer-specific mortality rate among males who have undergone hormone therapy in Japan is less than half of that in the United States (1); therefore, CAB has been administered for a long time in actual clinical practice. Thus, there are differences in the implementation of hormone therapy between Japan, Europe, and the United States. However, prostate cancer often becomes resistant to ADT after several years of its administration, resulting in CRPC (2). In Japan, the average male life expectancy has extended beyond 80 years, and the number of patients with CRPC is expected to increase, considering the widespread use of hormone therapy. In 2014, the use of the second-generation antiandrogen drug enzalutamide (ENZ), a novel androgen receptor signal inhibitor (ARSI); abiraterone (ABI), a CYP17A inhibitor; and cabazitaxel (CBZ), a new taxane anticancer drug were approved, which significantly changed CRPC treatment in Japan. ENZ competitively binds to the ligand-binding domain of androgen receptors and inhibits their migration to the cell nucleus (3). ABI is a potent inhibitor of CYP17A1, an enzyme that is important for androgen synthesis (4). ENZ and ABI improve radiographic progression-free survival (PFS) and overall survival (OS) compared to placebo in mCRPC both before and after docetaxel (DTX) treatment (5-7). These oral agents target androgen receptor signaling but are thought to have fewer adverse events, including myelosuppression, than DTX. DTX is myelosuppressive and induces severe neutropenia in Asian populations (8). Therefore, ENZ and ABI are widely used as standard first-line treatments for mCRPC in Japan. These agents exhibit cross-resistance to each other (9). The optimal administration sequence of ENZ and ABI is not fully understood, but it has been suggested that ABI followed by ENZ is superior for mCRPC in terms of PFS (10-14). In addition, although there was no difference in OS between ABI and ENZ, ENZ have a lower incidence of serious adverse events and a better prostate-specific antigen (PSA) response rate (15). This study aimed to investigate the current status of drug treatment selection for CRPC at Showa University and its affiliated institutions in Japan.

Patients and Methods

This retrospective study included 425 patients, diagnosed with CRPC at Showa University Hospital and its affiliated hospitals (Showa University Fujigaoka Hospital, Yokohama Kita Hospital, and Koto Toyosu Hospital) between January 2014 and December 2021, who were treated with any of the following four drugs: an ARSI (ABI or ENZ) or an antineoplastic drug (DTX or CBZ). Patients in whom ARSI was administered as an upfront treatment for metastatic castration-sensitive prostate cancer at the time of diagnosis were excluded. We investigated the actual treatment selection for the included patients, focusing on the order of administration of the four types of drugs (ABI, ENZ, DTX, and CBZ). The order of drug administration was evaluated using a Sankey diagram. The Sankey diagram was created using Google Looker Studio.

Our goal was to visualize the treatment sequence by creating a Sankey diagram.

The study design was approved by Showa University Institutional Review Board (No. 22-208-B), and the need for informed consent was obtained by an opt-out approach.

Results

A total of 184 patients (43.3%) used DTX and 241 (56.7%) used only ARSIs without DTX. Regarding the timing of administration, 65 patients (15.3%) used DTX as a first-line treatment before using ARSI, and 119 (28.0%) used it as a second-line treatment or later. CBZ was used in 95 patients (22.4%), and approximately half of the patients in whom DTX was administered were followed by the introduction of CBZ.

The treatment choices are shown in the Sankey diagram (Figure 1). One type of drug was used in 179 patients (42.1%), two in 108 (25.4%), three in 89 (20.9%), and four in 49 (11.5%) patients, with one type being the most common. In the patients who were treated with one type, all drugs used were ARSIs (ABI, 40 and ENZ, 139). The mean number of treatment lines was 2.0 (Figure 2).

The most commonly used drug in the first-line treatment was ENZ, which was administered in 58.4% of the patients. DTX was the most commonly used second-line drug, and CBZ was the most commonly used drug in both third- and fourth-line treatments (Figure 3). In the sequence of treatment up to the second-line treatment, the most common choice was ARSIs alone as the first-line treatment (n=179), followed by ARSI-secondary ARSI (n=96), ARSI-secondary DTX (n=85), DTX-secondary ARSI (n=59), and DTX-secondary CBZ (n=6). DTX was used in 65 patients as the first-line treatment, but the most common second-line treatment was ENZ in 37 patients (56.9%), followed by ABI in 22 (33.8%), and CBZ in 6 (9.2%) patients (Figure 4). Regardless of the timing of administration, all patients in whom DTX was administered proceeded to second-line treatment or later. However, in 241 patients in whom only ARSIs were administered without DTX, 139 of the 171 patients who selected ENZ as the first-line treatment (81.3%) completed the treatment with only first-line treatment.

Discussion

Although multiple treatment options are available for mCRPC, limited data are available to guide the optimal treatment sequences. Individualized treatment strategies should be considered in conjunction with patient preferences, age, comorbidities, drug tolerability, and economic status to guide treatment selection and sequencing. Although 3–25% of patients with mCRPC may develop primary resistance to ARSI therapy (3, 6, 16-18), the radiologic progression rather than the absence of PSA decline or progression within three months of treatment initiation is indicative of primary resistance to ARSI therapy

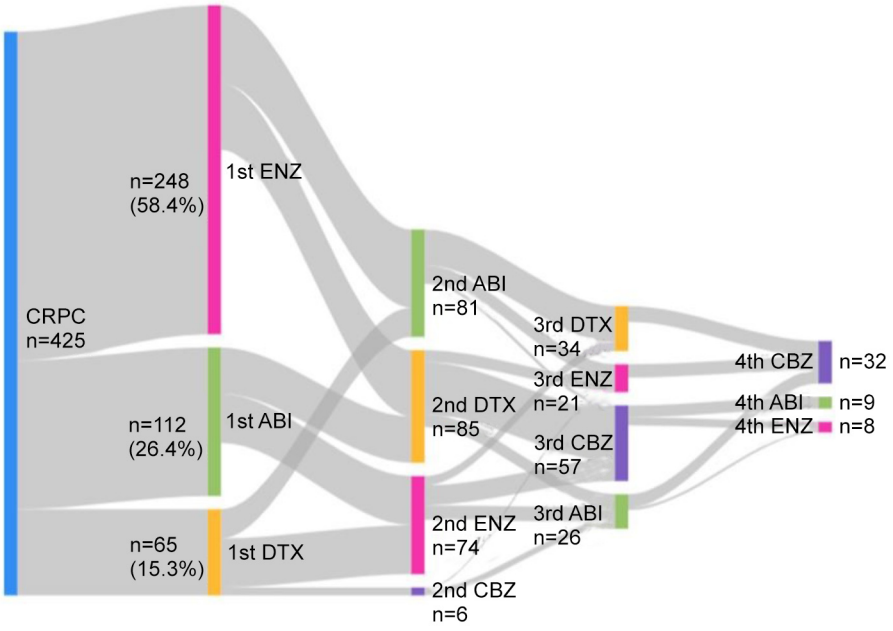

Figure 1. *Treatment sequences. The treatment choices are shown in the Sankey diagram. The length of the bar indicates the number of patients who chose treatment. Enzalutamide was more commonly chosen than anticancer chemotherapy for first-line treatment. ABI: Abiraterone acetate; ENZ: enzalutamide; DTX: docetaxel; CRPC: castration-resistant prostate cancer; CBZ: cabazitaxel.*

(19). In patients with mCRPC who have progressed on ADT for prostate cancer, treatment with androgen receptor axis-targeted therapy is preferred for the majority of patients. However, DTX can be considered for patients with a good performance status with chemotherapy tolerance, those suspected of ARSI resistance (*e.g.*, prior response to ADT for more than one year), and those with symptomatic or visceral metastatic disease. In a study by Okita *et al*. on treatment selection for mCRPC in clinical practice (20), chemotherapy (DTX) was used as the first-line treatment in 53% of patients after CRPC, and ARSIs were used in 47% of cases. In this study, chemotherapy was used as the first-line treatment in only 15.3% of patients, and ARSI was selected in approximately 85% of patients. ENZ was selected approximately in two-thirds of the patients in whom ARSI was selected as the first-line treatment. The most common number of treatment lines was one (42.9%), which consisted of ENZ (n=139) and ABI (n=40), but chemotherapy was not selected. In the future, it will be necessary to examine the prognosis of patients who received only one-line treatment and evaluate whether this treatment was insufficient, whether long-term control was possible, and whether first-line treatment alone was appropriate.

Study limitations. First, this study is retrospective. Second, prognosis according to the order of drug treatment has not been clarified. Finally, the backgrounds of patients who underwent treatment and the observation period were also unclear.

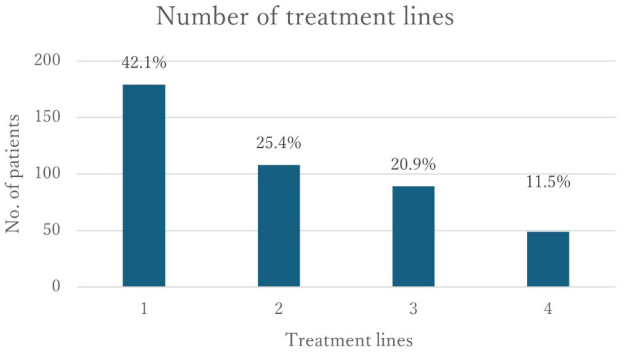

Figure 2. *Number of treatment lines. Most patients received one type of drug, with androgen receptor signal inhibitors being the most commonly administered. The mean number of treatment lines was 2.0.*

Patients with CRPC have various backgrounds, such as the presence or absence of metastasis at the time of prostate cancer diagnosis and the presence or absence of radical treatment, such as surgery or radiation therapy. The definition of recurrence after curative therapy differs depending on the type of treatment. Hatakeyama *et al*. reported that patients with a high tumor burden according to the CHAARTED study criteria at the time of diagnosis had a higher risk of progression to CRPC than those with a low tumor burden (21, 22). However, this study aimed to investigate the treatment selection in clinical practice.

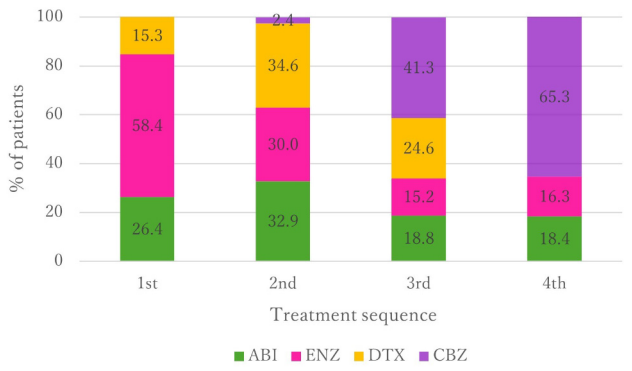

Figure 3. *Treatment sequence after the diagnosis of castration-resistant prostate cancer. The most commonly used drug in the first-line treatment was enzalutamide (ENZ), which was administered in 58.4% of the patients. Docetaxel (DTX) was the most commonly used second-line drug, and cabazitaxel (CBZ) was the most commonly used drug in both third- and fourth-line treatments. ABI: Abiraterone acetate.*

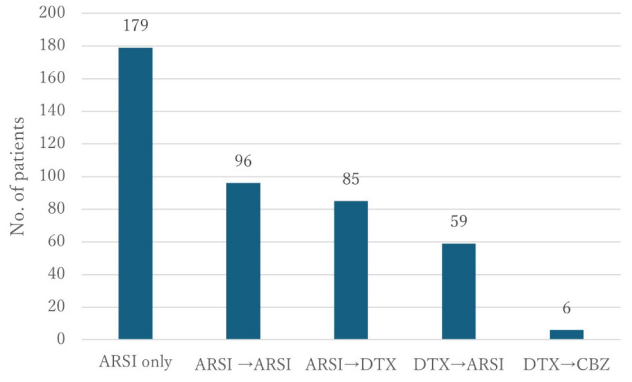

Figure 4. *Treatment options up to the first and second line. In the sequence of treatment up to the second-line treatment, the most common choice was androgen receptor signal inhibitors (ARSIs) alone as the first-line treatment (n=179). DTX: Docetaxel; CBZ: cabazitaxel.*

Although a prognostic investigation will be necessary in the future, it is significant that the actual treatment selection, including the order of ABI and ENZ administration, has been clarified. Furthermore, treatment selection may change depending on the historical background. It is believed that the backgrounds of patients with CRPC in the latter half of the survey period (around 2014) differed from those in 2020. It is presumed that the participants in 2014 included those who had been receiving only DTX for a long time, and little evidence is available regarding patients who had been receiving anti-androgen drugs or steroid therapy. In addition, this study did not include cases of prior ARSI administration for metastatic hormone-sensitive prostate cancer.

Currently, sequential treatment with ENZ and ABI is not mandatory, as several other promising drugs with different mechanisms (*e.g.*, radium-223 and olaparib) are available. Continuous use of these oral ARSIs is not always required (23). The CARD study showed that the CBZ group had improved prognosis compared with the ARSI group in the third-line treatment of patients with mCRPC who had a history of DTX treatment and progressed with ARSI (ABI or ENZ) (24). Although the optimal order is unclear, it is desirable to administer ABI as early as possible and then administer DTX and CBZ early. However, this is not necessarily the case in clinical practice, although there may be differences in historical backgrounds. Bjartell *et al*. stated that patient characteristics influence treatment selection for mCRPC and recommended ABI for older patients and those with low Gleason scores, DTX for younger patients with advanced disease, and ENZ for patients with few metastases and a good performance status (25). In addition, ABI requires the combination of steroids, and the management of side effects may be more complicated compared with ENZ. It is believed that patient characteristics also play a large role in treatment selection in this study, but further investigation is needed into the individual patient backgrounds and reasons for selection.

Conclusion

In this study, which investigated the rear-world treatment of drug selection for mCRPC in Japan, the most commonly used drug classification in the first-line treatment of mCRPC at our institution and affiliated institutions was ARSIs, with ENZ being the most commonly used. Currently, the use of upfront ARSIs has become the standard treatment, and a variety of treatment options are available, including the use of radium-223 and poly (ADP-ribose) polymerase inhibitors; therefore, drug treatment options are different, and further investigation is required regarding patient background and prognosis. Although the optimal treatment sequence for CRPC has not been determined, ENZ was the most commonly selected agent in our study. Its ease of administration and management may have influenced this choice.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Kazuhiko Oshinomi: Methodology; Software; Data curation; Writing–original draft; Writing–review & editing; Visualization. Toshiki Mugita: Visualization; Data curation. Tatsuki Inoue: Data curation. Madoka Omizu: Data curation. Motoki Yamagishi: Data curation. Yoshihiro Nakagami: Data curation; Supervision; Investigation. Masakazu Nagata: Supervision. Hideaki Shimoyama: Data curation. Michiya Ota:

Data curation. Jun Morita: Supervision. Haruaki Sasaki: Supervision. Eiji Matsubara: Data curation. Katsuyuki Saito: Data curation; Supervision. Kohzou Fuji: Supervision. Masashi Morita: Data curation; Supervision. Takashi Fukagai: Supervision; Project administration.

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