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Real-World Experience with Triplet Therapy for High-Volume Metastatic Castration-Sensitive Prostate Cancer: A Retrospective Cohort Study from a Japanese Academic Hospital

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Background: Prostate cancer (PCa) significantly contributes to male cancer mortality. Triplet therapy shows promise for metastatic castration-sensitive prostate cancer (mCSPC), but real-world data are limited. This study aimed to evaluate the clinical outcomes of triplet therapy in real-world patients with mCSPC at an academic hospital in Japan.

Methods: We retrospectively analyzed the efficacy and safety of triplet therapy, comprising androgen deprivation therapy, docetaxel, and darolutamide, in patients with mCSPC at Nippon Medical School Hospital. Clinical outcomes, adverse events (AEs), prostate-specific antigen (PSA) responses, and progression to castration-resistant prostate cancer were assessed.

Results: Between January 2023 and June 2024, we identified 14 Japanese patients with mCSPC who received triplet therapy. All patients presented with synchronous high-volume metastases as defined by the CHAARTED criteria. The median follow-up period was 7.9 months. In terms of efficacy, all 14 patients achieved PSA reduction of > 90%, while 13 of them achieved reductions of > 99%. AEs were reported in all patients, with grade 3 or higher AEs occurring in 10 patients. One patient permanently discontinued treatment and 4 patients temporarily interrupted therapy due to AEs. During follow-up, biochemical progression was observed in 2 patients and radiological progression in 2 patients. Subsequent therapies were selected based on each patient's clinicopathological and genetic characteristics, with considerable variability in treatment approaches following progression.

Conclusions: While PSA responses were favorable and tolerability was generally high, progression patterns and subsequent therapies varied widely, highlighting the need for close monitoring and individualized treatment in patients with mCSPC receiving triplet therapy.

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Key words: prostate cancer, drug therapy, metastatic prostate cancer, chemotherapy

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer among men and ranks as the sixth leading cause of cancer-related deaths in Japan[1]. Early-stage PCa is often asymptomatic, leading to delayed detection, particularly in patients who do not undergo prostate-specific antigen (PSA) screening[2]. Epidemiological studies report that metastatic castration-sensitive prostate cancer (mCSPC) is present in 4-8% of patients at initial diagnosis, with a generally poor prognosis[3]. Therefore, thorough

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disease assessment and the implementation of appropriate treatment strategies are critical in managing mCSPC.

In recent years, treatment advancements for mCSPC have resulted in a shift toward combination therapies. Doublet therapy, which involves adding a single agent such as abiraterone[4], apalutamide[5], enzalutamide[6], or docetaxel[7], to androgen deprivation therapy (ADT), has been shown to improve overall survival (OS) and disease progression. More recently, triplet therapy—which combines ADT, an abiraterone[8] or darolutamide[9], and docetaxel—has demonstrated improved OS compared to doublet therapy with docetaxel in randomized controlled trials involving patients with mCSPC. These advancements in combination therapies introduce the concept of intensified treatment by combining ADT and cytotoxic chemotherapy, offering novel and promising approaches to managing PCa.

The ARASENS trial, a phase 3 study, compared the combination of ADT, docetaxel, and darolutamide with ADT, docetaxel, and placebo in 1,306 patients with mCSPC, demonstrating a significant improvement in OS[9]. Subgroup analysis based on the CHAARTED criteria further confirmed that triplet therapy improves OS in mCSPC[10]. Based on the results of this trial, triplet therapy including darolutamide for mCSPC has been covered by insurance in Japan since 2023. Notably, while clinical trials typically enroll patients in relatively good health, real-world clinical practice often involves patients with severe comorbidities, which can impact treatment outcomes and tolerability[11]. To optimize mCSPC management for patients with poor prognoses, it is essential to integrate both clinical trial results and real-world data. To date, only few studies have reported on real-world data regarding triplet therapy for mCSPC[12,13]. As such data continue to emerge, uro-oncologists will gain a more comprehensive understanding of the clinical efficacy and safety of triplet therapy in diverse patient populations. Therefore, this study aimed to evaluate the clinical outcomes of the initial experience with triplet therapy in real-world patients with mCSPC at an academic hospital in Japan.

Materials and Methods

Study Design and Methods

We conducted a retrospective evaluation of clinical outcomes in patients with mCSPC who received triplet therapy consisting of ADT, docetaxel, and darolutamide at Nippon Medical School Hospital (NMSH) between January 2023 and June 2024. Using a retrospective cohort design, we analyzed treatment outcomes and detailed follow-up data of previously treated patients. Eligibility for triplet therapy at NMSH was based on the CHAARTED criteria for high-volume mCSPC, defined as either (1) the presence of visceral metastases or (2) at least four bone lesions, with one or more lesions located beyond the spine and pelvis[7]. After initiating ADT and darolutamide (600 mg [two 300 mg tablets] taken twice daily with food), patients received docetaxel at a standard dose of 70 mg/m^2 every 3 weeks. Dose reductions and adjustments to the dosing schedule were allowed at the discretion of the treating physician based on patient tolerability. ADT included orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonists or antagonists as part of the regimen. The follow-up period was measured from the initiation of ADT, and only patients who promptly initiated darolutamide and docetaxel after starting ADT were included. Cases of progression to castration-resistant prostate cancer (CRPC) were identified, and their clinical courses were thoroughly assessed.

Ethics Declaration

This study was approved by the Ethics Committee of NMSH (approval number: B-2024-942) and was conducted in accordance with the tenets of the Declaration of Helsinki. The requirement for informed consent was waived by the Ethics Committee of the NMSH due to its retrospective design and lack of intervention. However, all participants had the opportunity to opt out of the study through the NMSH Ethics Committee website.

Evaluations

Data on demographic characteristics, clinicopathological features, treatment strategies, and follow-up outcomes were obtained from electronic medical records. Performance status (PS) was evaluated using the Eastern Cooperative Oncology Group (ECOG) scale to provide a comprehensive assessment of patients' health status. PSA nadir was defined as the lowest PSA value recorded during follow-up. For patients with shorter follow-up periods where PSA levels were still declining, the latest recorded PSA value was used as the nadir. The PSA reduction rate was calculated as the percentage decrease from the initial PSA level to the PSA nadir. CRPC was defined as either biochemical progression (defined as a PSA increase of ≥ 50% from the nadir, with PSA levels >2 ng/mL after three consecutive rises at least 1 week apart) or radiological progression (defined as new lesions on bone scintigraphy or soft tissue lesions detected per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1)[14]. Imaging assessments were conducted every 3-6

Table 1 Patient demographic and clinical characteristics at baseline

Parameters	n =14	
Age, median (IQR)	72	66.3-75.5
ECOG-PS, n (%)		
0	12	85.7
1	2	14.3
PSA level, (ng/mL), median (IQR)	371	121-1,267
Hb level, (g/dL), median (IQR)	12.8	10.7-14
ALP level, (U/L), median (IQR)	219	78-687
Gleason score, n (%)		
8	4	28.6
9	10	71.4
EOD score, n (%)		
0	0	0.0
1	2	14.3
2	4	28.6
3	5	35.7
4	3	21.4
Metastatic stage, n (%)		
M1a	4	28.6
M1b	14	100
M1c	5	35.7
Type of metastatic disease, n (%)		
Synchronous	14	100
Metachronous	0	0.0
CHAARTED criteria, n (%)		
High-volume	14	100
Low-volume	0	0.0
ADT, n (%)		
Orchiectomy	1	7.1
LHRH agonist	4	28.6
LHRH antagonist	9	64.3

n: number of patients, IQR: interquartile range, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, PSA: prostate-specific antigen, EOD: extent of disease, ADT: androgen deprivation therapy, LHRH: luteinizing hormone-releasing hormone

months after initiation of triplet therapy. Adverse events (AEs) were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[15]. Continuous parametric variables are reported as medians with interquartile ranges (IQR). Statistical analyses were performed using JMP 16.1.0 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

Table 1 summarizes the baseline demographic and clinical characteristics of 14 Japanese patients with mCSPC who were treated with triplet therapy incorporating darolutamide at NMSH. The median age at treatment initiation was 72 years (IQR: 66.3-75.5 years). Among these patients, 12 (85.7%) had an ECOG-PS of 0, while 2 (14.3%) had a PS of 1. The median PSA level was 371 ng/mL (IQR: 121-1,267 ng/mL). All patients were diagnosed via prostate biopsy. Gleason scores (GS) of 8 were observed in 4 patients (28.6%), while 10 patients (71.4%) had a GS of 9. At treatment initiation, all patients had synchronous mCSPC and were classified as high-volume according to the CHAARTED criteria. Regarding ADT, 9 patients (64.3%) received LHRH antagonists, 4 (28.6%) received LHRH agonists, and 1 patient (7.1%) underwent surgical castration.

Safety Profile

Table 2 provides an overview of AEs and drug tolerability in patients treated with triplet therapy. All 14 patients (100%) experienced AEs related to the therapy, with grade 3 or higher AEs (according to CTCAE) occurring in 10 patients (71.4%). **Table 3** summarizes the spe-

Table 2 Adverse events and drug tolerability

Parameters	n = 14	
Any adverse event, n (%)	14	100
Worst grade, n (%)		
1	2	14.3
2	2	14.3
3	5	35.7
4	5	35.7
Treatment discontinuation, n (%)	1	7.1
Treatment interruption/postponement, n (%)	4	28.6
GCSF during chemotherapy, n (%)	9	64.3

n: number of patients, G-CSF: granulocyte colony-stimulating factor

Table 3 Summary of adverse events during triplet therapy

Specification of adverse events	n = 14			
	Grade 3-4, n (%)		Any grade, n (%)	
Neutropenia	9	64.3	14	100
Anemia	4	28.6	12	85.7
Thrombocytopenia	1	7.1	5	35.7
Fatigue	1	7.1	3	21.4
Eruption	1	7.1	1	7.1
Alopecia	0	0.0	11	78.6
Anorexia	0	0.0	9	64.3
Edema	0	0.0	1	7.1
Stomatitis	0	0.0	1	7.1
Gastrointestinal bleeding	0	0.0	1	7.1
Dysgeusia	0	0.0	1	7.1

n: number of patients

cific AEs observed during triplet therapy. Severe grade 3 or higher AEs included neutropenia in 9 patients (64.3%) and anemia in 4 patients (28.6%). Prophylactic granulocyte colony-stimulating factor (G-CSF) was administered to 9 patients (64.3%) due to neutropenia, and treatment delays occurred in 4 patients (28.5%) who could not maintain the 3-week treatment interval. One patient (7.1%) experienced a grade 4 skin rash, leading to discontinuation of docetaxel.

Efficacy Profile

The median follow-up period was 7.9 months (IQR: 6.0-14.4 months), and the treatment efficacy of triplet therapy during this period is summarized in **Table 4**. The median PSA nadir was 0.18 ng/mL (IQR: 0.03-0.55 ng/mL), with a median PSA reduction rate of 99.9% (IQR: 99.7-100%). All patients achieved a PSA reduction of > 90%, and 10 patients (71.4%) reached PSA levels below 0.2 ng/mL.

Recurrence after Triplet Therapy

During the follow-up period, the condition in 4 patients (28.6%) progressed to CRPC, with a median time to progression of 13.8 months (IQR: 7.7-17.4 months) from the initiation of treatment. Of these, 2 patients experienced biochemical progression, while 2 had radiological progression. Details of the patients with disease progression are provided below (**Fig. 1a-d**).

Case Presentations

Case 1 (Fig. 1a)

A 72-year-old man presented with a PSA level of 2,067 ng/mL, prompting a transrectal sextant prostate biopsy. The biopsy revealed a GS of 4+5=9. Imaging studies showed multiple bone metastases, classified as EOD 4. The pretreatment diagnosis was PCa, cT2bN0M1b, with high-volume metastases according to the CHAARTED criteria. Based on this, the treatment approach involved triplet therapy, including darolutamide. Treatment was initiated with an LHRH antagonist and darolutamide (1,200 mg/day), followed by the addition of docetaxel (70 mg/m^2, administered tri-weekly) after 1 month. During treatment, AEs included grade 4 neutropenia, for which prophylactic G-CSF was administered. Addition-

Table 4 Evaluation of treatment efficacy during triplet therapy

Parameters	n = 14	
Follow-up, (months), median (IQR)	7.9	6.0-14.4
PSA nadir, (ng/mL), median (IQR)	0.18	0.03-0.55
PSA nadir<0.2 ng/mL, n (%)	10	71.4
PSA decrease, (%), median (IQR)	99.9	99.7-100
PSA decrease>90%, n (%)	14	100
PSA decrease>99%, n (%)	13	92.9
Progression to CRPC, n (%)	4	28.6
PSA recurrence	2	14.3
Radiological recurrence, n (%)	2	14.3

n: number of patients, IQR: interquartile range, PSA: prostate-specific antigen, CRPC: castration-resistant prostate cancer

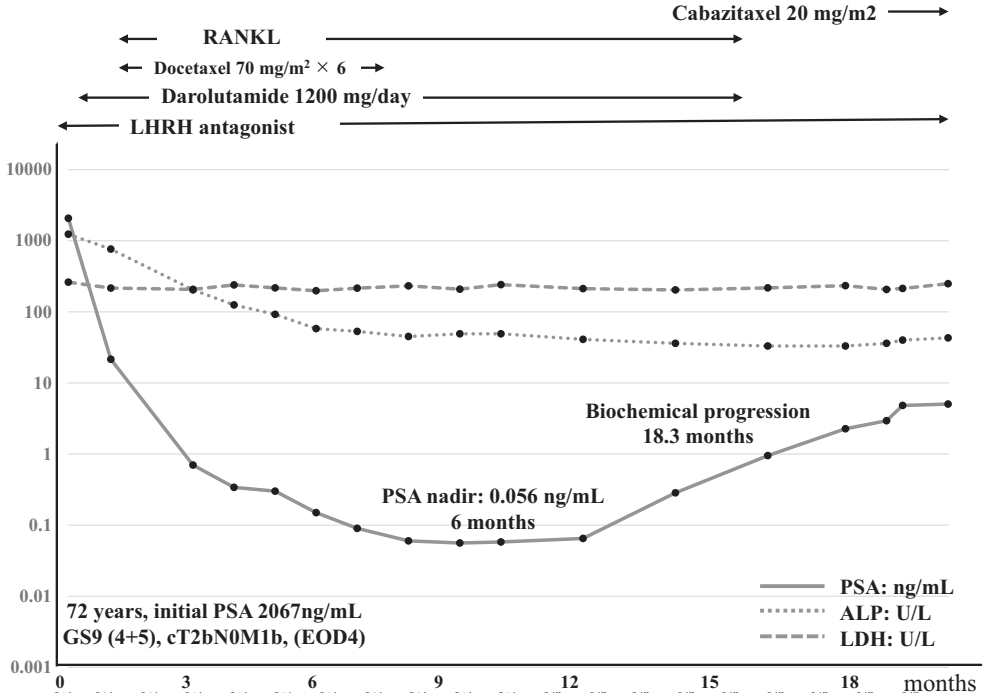

Fig. 1a Clinical course of Case 1

A 72-year-old man with an initial PSA of 2,067 ng/mL and a Gleason score of 9 (4+5) is diagnosed with PCa (cT2bN0M1b, high volume). He receives triplet therapy with an LHRH analog, darolutamide, and docetaxel. Treatment-related adverse events include grade 4 neutropenia and grade 2 anemia and fatigue. After achieving a PSA nadir of 0.056 ng/mL at 6 months, biochemical recurrence occurs at 18.3 months. Following recurrence, comprehensive genomic profiling finds no genotype-matched therapies, and the patient is currently on cabazitaxel.

PCa: prostate cancer, PSA: prostate-specific antigen, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, GOT: glutamic oxaloacetic transaminase, γGTP: gamma-glutamyl transpeptidase, GS: Gleason score, EOD: extent of disease, LHRH: luteinizing hormone-releasing hormone, RANKL: receptor activator of nuclear factor kappa B ligand, PARP: poly (ADP-ribose) polymerase, CT: computed tomography, EP: etoposide and cisplatin chemotherapy, CGP: comprehensive genomic profiling, G-CSF: granulocyte colony-stimulating factor

ally, the patient developed grade 2 anemia and fatigue, requiring a red blood cell transfusion. Six months after treatment initiation, the patient achieved a PSA nadir of 0.056 ng/mL. However, biochemical recurrence was observed 18.3 months after treatment initiation. Comprehensive genomic profiling (CGP) was conducted post-recurrence, but no genotype-matched therapy options were identified. The patient is currently receiving cabazi-

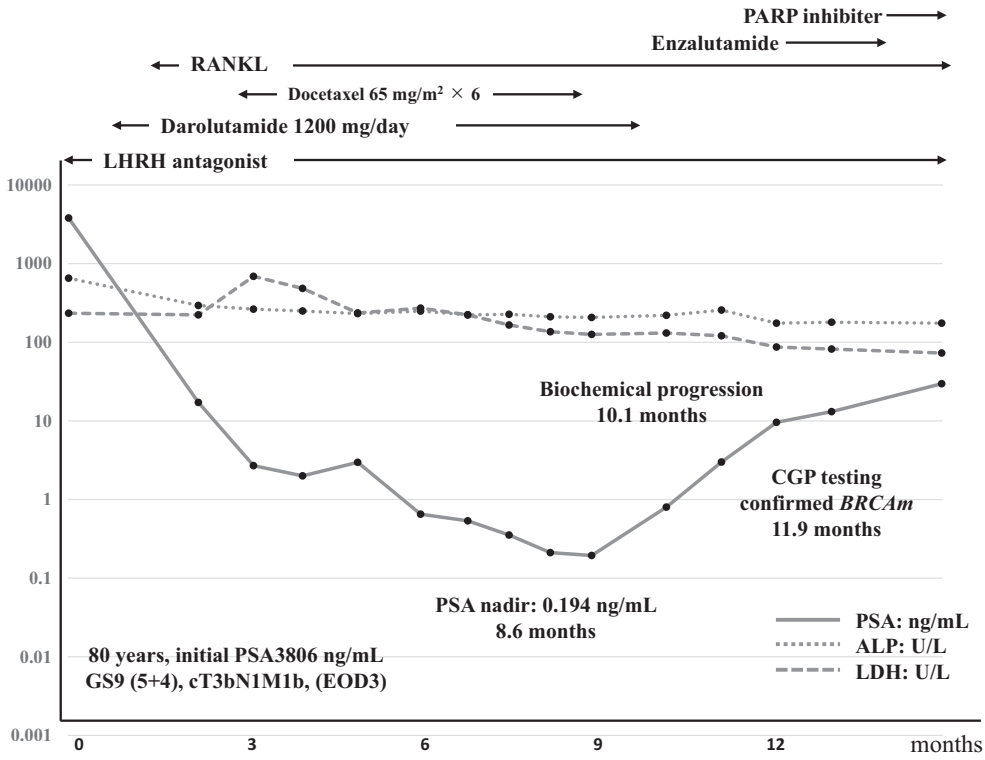

Fig. 1b Clinical course of Case 2

An 80-year-old man with an initial PSA of 3,806 ng/mL and a Gleason score of 9 (5+4) is diagnosed with high-volume PCa (cT3bN1M1b). He receives triplet therapy with an LHRH analog, darolutamide, and docetaxel (65 mg/m² monthly). Treatment-related adverse events include grade 3 neutropenia and grade 1 alopecia. The patient achieved a low PSA level (<0.2 ng/mL) but experiences PSA progression at 10.1 months. Post-recurrence, enzalutamide is administered, and CGP testing shows BRCA2 mutation positivity. He is currently on a poly (ADP-ribose) polymerase (PARP) inhibitor.

taxel (20 mg/m^2, administered tri-weekly) following recurrence.

Case 2 (Fig. 1b)

An 80-year-old man presented with a PSA level of 3,806 ng/mL, leading to a transrectal sextant prostate biopsy. The biopsy revealed a Gleason score of 5+4=9. Radiological findings showed regional lymph node metastasis and multiple bone metastases (EOD 3). The patient was diagnosed with PCa, cT3bN1M1b, and classified as high volume according to the CHAARTED criteria. Our team chose triplet therapy, including darolutamide. Treatment began with an LHRH antagonist and darolutamide (1,200 mg/day), and 2 months later, docetaxel (65 mg/m^2, administered tri-weekly) was added. The docetaxel dose was reduced due to the patient's advanced age, at the discretion of the attending physician. During treatment, AEs included grade 3 neutropenia, for which prophylactic G-CSF was administered, and grade 1 alopecia. However, 10.1 months into treatment, biochemical progression was observed. After recurrence, enzalutamide was administered, and CGP testing revealed BRCA2 positivity. The patient is currently receiving a poly (ADP-Ribose) polymerase (PARP) inhibitor as post-progression therapy.

Case 3 (Fig. 1c)

A 70-year-old man presented with a PSA level of 126.3 ng/mL, leading to a transrectal sextant prostate biopsy. The biopsy revealed a GS of 4+5=9. Radiological findings showed regional lymph node involvement, widespread bone metastases (EOD 4), and multiple lung metastases. The patient was diagnosed with PCa, cT3bN1M1b+c, and classified as high volume according to the CHAARTED criteria. Treatment began with an LHRH agonist and darolutamide (1,200 mg/day), followed by the addition of docetaxel (70 mg/m^2, administered tri-weekly) after 4 months. During treatment, AEs included grade 3 neutropenia, as well as grade 1 anemia, stomatitis, and alopecia. The patient maintained a PSA level of < 0.008 ng/mL throughout treatment. However, 14 months after treatment initiation, liver dysfunction developed, and subsequent imaging confirmed multiple liver lesions. A percu-

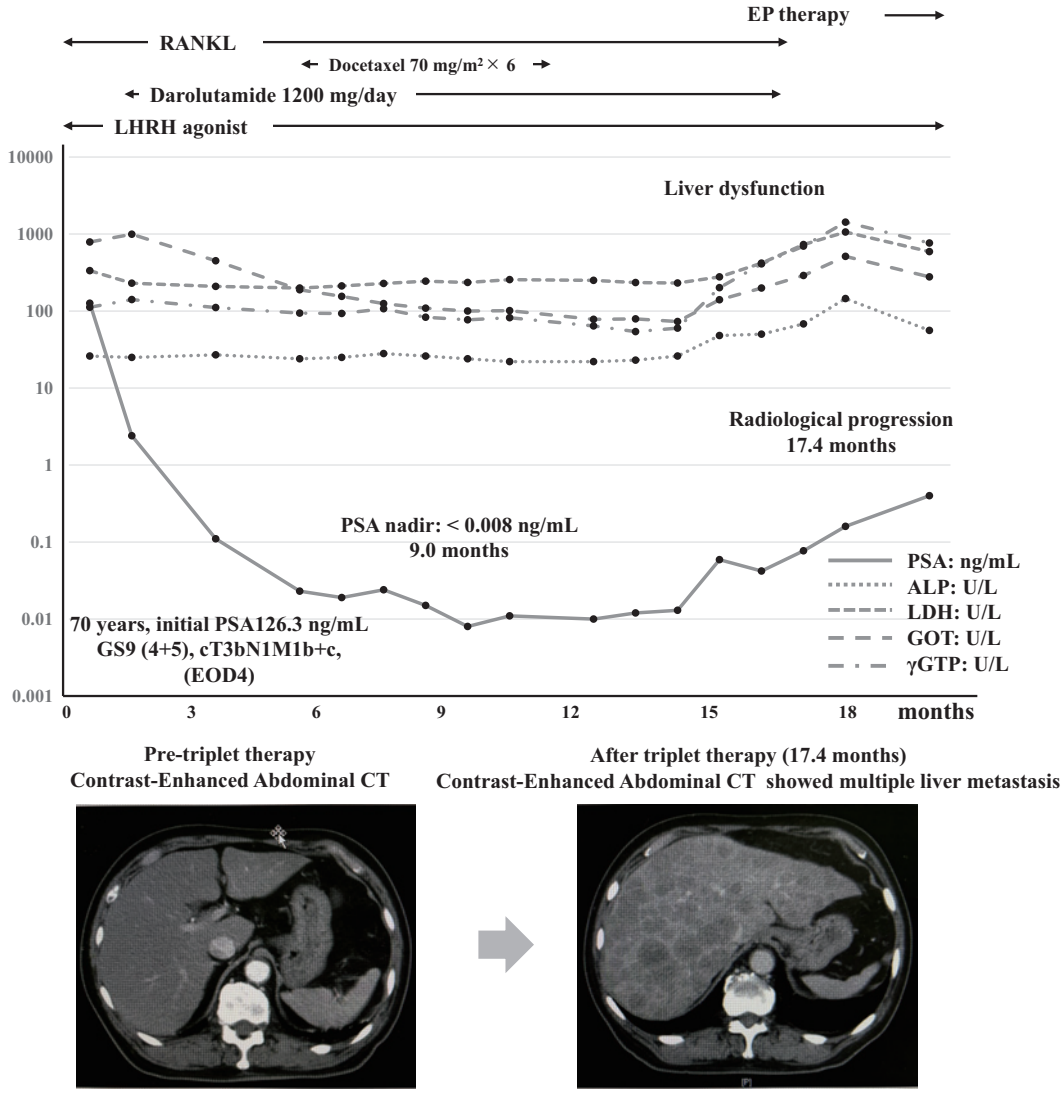

Fig. 1c Clinical course of Case 3

A 70-year-old man with an initial PSA of 126.3 ng/mL and a Gleason score of 9 (4+5) with IDCP is diagnosed with high-volume PCa (cT3bN1M1b+c). He receives triplet therapy with an LHRH agonist, darolutamide, and docetaxel. Treatment-related adverse events include grade 3 neutropenia, grade 1 anemia, stomatitis, and alopecia. The patient achieved a low PSA level (<0.008 ng/mL) but develops liver dysfunction at 14 months, with imaging revealing hepatic masses. A liver biopsy confirms neuroendocrine differentiation, and CGP testing finds no genotype-matched therapies. He is currently receiving etoposide plus cisplatin.

taneous biopsy of the liver lesions revealed neuroendocrine differentiation of the PCa. CGP performed in parallel did not identify any suitable genotype-matched therapy options. The patient is currently receiving etoposide plus cisplatin therapy following disease progression.

Case 4 (Fig. 1d)

A 69-year-old male presented with a PSA level of 343 ng/mL, prompting a transrectal sextant prostate biopsy. The biopsy results showed a GS of 4+5=9. Imaging revealed multiple lymph node metastases, extensive bone metastases (EOD3), and lung metastases. The pretreatment diagnosis was PCa, cT3bN1M1a+b+c, classified as high volume according to the CHAARTED criteria. Our team decided on a treatment plan involving triplet therapy with darolutamide. Treatment was initiated with surgical castration and darolutamide (1,200 mg/day), followed by docetaxel (70 mg/m^2, administered tri-weekly) after 1 month. During treatment, AEs included grade 4 neutropenia, for which prophylactic G-CSF was administered. Additional AEs included grade 1 alopecia, loss of appetite, and anemia. After treatment initiation, the patient achieved a PSA nadir of 1.1 ng/mL; however, progression of multiple bone metastases was suspected 6.9 months after treatment initiation. PSA levels showed a

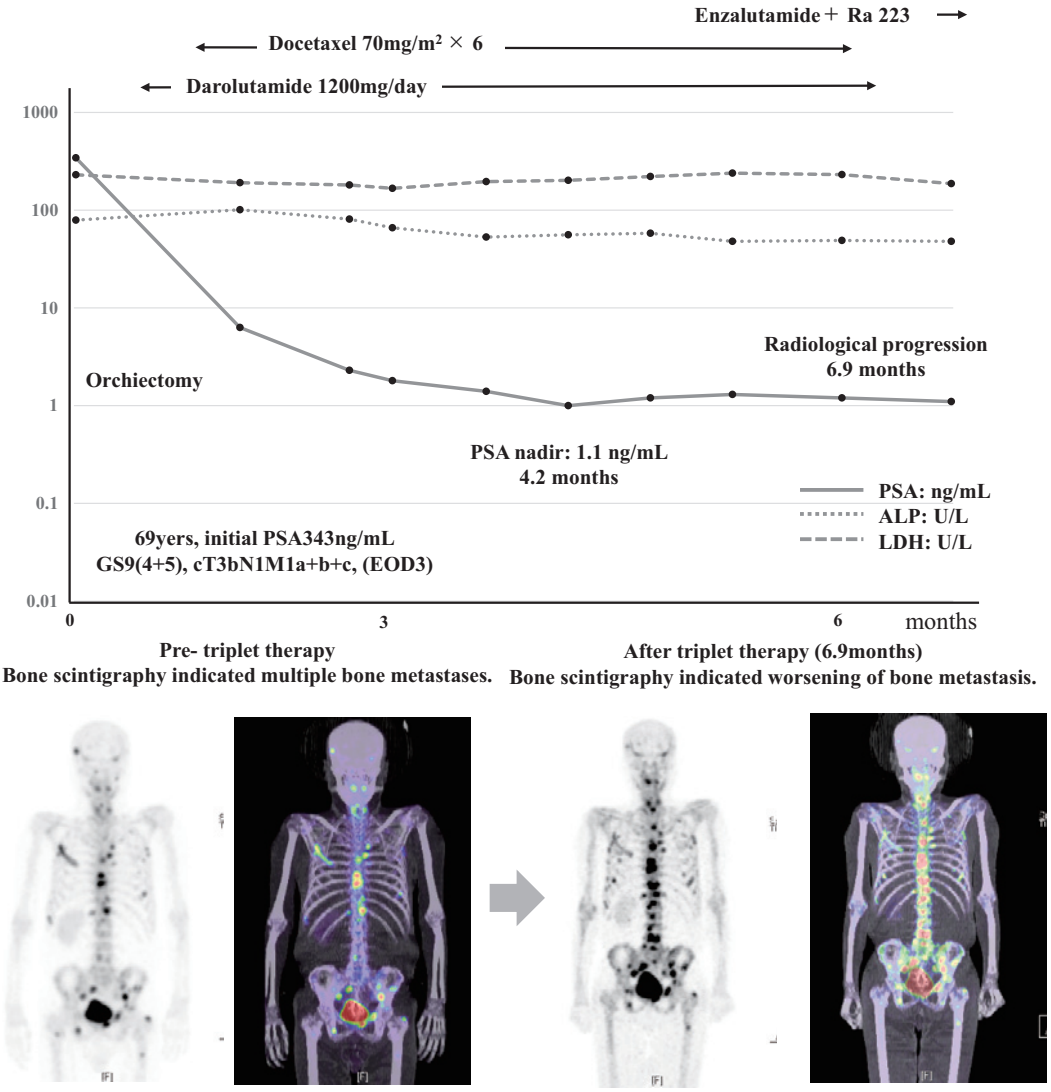

Fig. 1d Clinical course of Case 4

A 69-year-old man with an initial PSA level of 343 ng/mL and a Gleason score of 9 is diagnosed with high-volume PCa (cT3bN1M1a+b+c, based on the CHAARTED criteria) involving lymph nodes, bones, and lungs. He is treated with triplet therapy: surgical castration, darolutamide (1,200 mg/day), and docetaxel (70 mg/m² tri-weekly). The treatment results in a PSA nadir of 1.1 ng/mL, however, the progression of bone metastases was suspected after 6.9 months. Adverse events include grade 4 neutropenia (managed with G-CSF), mild alopecia, appetite loss, and anemia. Post-progression, the patient is being treated with enzalutamide and Radium-223.

slow upward trend, and post-recurrence therapy with enzalutamide and Radium-223 is currently being administered.

Subsequent therapy after progression was determined during our team conference. For patients with biochemical progression, cabazitaxel was administered in one case, while a PARP inhibitor was used after enzalutamide in another. For patients with radiologic progression, etoposide plus cisplatin therapy was employed in one case with neuroendocrine differentiation, and enzalutamide combined with Radium-223 dichloride was administered in one case with bone metastases. Based on these findings, all four patients who progressed showed a favorable decline in PSA levels following triplet therapy. However, each patient exhibited different progression patterns, requiring individualized treatment strategies for subsequent therapy.

Discussion

We evaluated the initial experience with triplet therapy, including darolutamide, in 14 patients with synchronous and high-volume mCSPC at a single academic hospital in Japan. Our results demonstrated that triplet therapy achieved a favorable PSA response and high tolerability

in these patients. However, progression to CRPC occurred in 4 patients (28.6%), whose clinical courses required varied subsequent treatment approaches.

Reported studies on triplet therapy, including darolutamide, for mCSPC were summarized (**Table 5**). The ARASENS study, a phase III trial, compared the combination therapy of darolutamide, ADT, and docetaxel with ADT and docetaxel in 1,306 patients with mCSPC[9]. The primary endpoint in this trial showed a significant 32.5% reduction in the risk of death in the darolutamide group compared to that in the placebo group (hazard ratio 0.68, $p < 0.001$). Subgroup analysis further demonstrated improved OS and radiological progression-free survival in the darolutamide group, irrespective of the CHAARTED volume classification[10]. Furthermore, the ARASENS trial included 148 Japanese patients, who also exhibited extended OS[16]. Based on these findings, triplet therapy has been adopted in Japan for mCSPC since 2023. However, real-world data on triplet therapy remain limited. A report from Austria examined 97 patients treated with triplet therapy, including 17 patients receiving darolutamide. Among these, 83.5% had high-volume disease, diagnosed via conventional imaging (48.9%) or prostate-specific membrane antigen positron emission tomography (51.1%)[12]. In this cohort, the median PSA nadir was 0.13 ng/mL, with a PSA reduction rate of 99.9%, demonstrating a robust PSA response. In Japan, the sole real-world study analyzed 45 patients with mCSPC, of whom 37 (82.2%) had high-volume disease and 8 (17.8%) had low-volume disease. Triplet therapy achieved a PSA decline of ≥ 90% in 43 patients (95.6%), with imaging confirming a treatment response in 44 patients (97.8%). Additionally, 37 patients (82.2%) exhibited a PSA reduction of ≥ 99%[13]. In our cohort, all patients presented with synchronous, high-volume mCSPC, a condition known for its high resistance to drug therapy[17]. The median PSA reduction rate was 99.9%, with all patients achieving a PSA reduction of > 90%, reflecting favorable treatment outcomes. Despite this, 4 patients (28.6%) progressed to CRPC. While these patients demonstrated a favorable PSA response, the median time to progression was only 13.8 months. These findings underscore the importance of recognizing that even patients with a favorable PSA response to triplet therapy for mCSPC remain at risk for early disease progression. Uro-oncologists should be vigilant in monitoring and managing such cases.

The ARASENS trial reported an overall AE incidence of 99.5% in the triplet therapy group, with grade 3 or higher AEs occurring in 70.2% of patients[9]. Treatment discontinuation due to AEs was observed in 21.5% of patients. Subgroup analysis based on the CHAARTED volume classification revealed AE incidences of 99.6% in the high-volume group and 99.4% in the low-volume group[10]. Grade 3 or higher AEs were observed in 69.1% of the high-volume group and 74.1% of the low-volume group, with treatment discontinuation rates of 21.1% and 22.7%, respectively. These findings indicate no significant differences in AE incidence or treatment discontinuation rates between high- and low-volume groups. Real-world data from Japan on triplet therapy demonstrated an AE incidence of 86.7%, with grade 3 or higher AEs in 55.6% of patients[13]. Treatment discontinuation due to AEs occurred in 11.1% of patients. These results highlight the critical importance of prophylactic administration of G-CSF for the safe and sustained delivery of triplet therapy in Japanese patients with mCSPC, similar to the approach used in Docetaxel therapy for mCRPC[18]. In our analysis, AEs were reported in 100% of patients, with grade 3 or higher AEs occurring in 71.4%, and treatment discontinuation in 7.1%. Notably, 64.3% of our cohort, consisting of Japanese patients with synchronous, high-volume mCSPC, successfully managed triplet therapy with the support of prophylactic G-CSF. These findings further underscore the role of G-CSF in maintaining the safety and continuity of triplet therapy in this population.

Achieving long-term survival in mCSPC necessitates the strategic implementation of effective sequencing therapy[19]. In the ARASENS trial, subsequent treatments for patients who progressed after triplet therapy were determined by the treating physician and included abiraterone (35.6%), enzalutamide (15.2%), cabazitaxel (18.0%), docetaxel (18.0%), and Ra-223 (6.9%)[20]. Furthermore, post-hoc analysis of the trial explored patient outcomes based on these follow-up treatments[18]. This analysis primarily focused on patients who relapsed within a short period; however, it revealed no clear prognostic differences among the treatment options. Currently, the optimal approach to managing CRPC following progression on triplet therapy remains unclear, emphasizing the need for further research. In our cohort, 4 patients (28.6%) progressed to CRPC within a relatively short time, with each showing distinct progression patterns that required individualized treatment strategies. Patients requiring triplet therapy often present with more aggressive disease features. Therefore, a multidisciplinary evaluation of clinical status, including imaging and blood tests, is crucial to identify the most appropriate treatment strategy for patients undergoing triplet therapy for mCSPC.

Table 5 Reported studies of triplet therapy including darolutamide for metastatic castration-sensitive prostate cancer

No	Author		Year	n	H-volume/ L-volume, n	PSA reduction rate Median, (%)	PSA reduction >90%, n (%)		PSA<0.2, n (%)		Any AEs, n (%)		AE grade>3, n (%)		AE Treatment discontinuation, n (%)	
1	Smith et al.	ARASENS Phase-3	2022	651	497/154	-	553	(84.9)	438	(60.2)	649	(99.5)	458	(70.4)	140	(21.5) *
2	Uemura et al.	ARASENS Phase-3 Japan data	2023	63	48/15	-	-	-	-	-	63	(100)	58	(92.1)	20	(31.7) **
3	Kafka et al.	Real-world from Austria	2024	17	13/4	99.86	-	-	-	-	10	(58.8)	2	(11.8)	1	(5.9) ***
4	Urabe et al.	Real-world from Japan	2024	45	37/8	99.97	43	(95.6)	28	(62.2)	39	(86.7)	25	(55.6)	5	(11.1) †
5	Our study	Real-world from Japan	2024	14	14/0	99.9	14	(100)	10	(71.4)	14	(100)	10	(71.4)	1	(7.1) ††

* The number of cases leading to permanent discontinuation of the trial agent due to AEs was 88 (13.5%) for darolutamide and 52 (8.0%) for docetaxel.

** In the Japanese cohort, the number of cases leading to permanent discontinuation of the trial agent due to AEs was 11 (17.5%) for darolutamide and 9 (14.3%) for docetaxel.

*** One patient died due to multiorgan failure.

† The specific side effects leading to discontinuation were as follows: febrile neutropenia in 2 patients (40.0%), malaise in 1 patient (20.0%), pneumonitis in 1 patient (20.0%), and limb edema in 1 patient (20.0%).

†† In one case of severe rash, docetaxel treatment was discontinued.

n: number of patients, H-volume: high volume by CHAARTED criteria, L-volume: low volume by CHAARTED criteria, PSA = prostate-specific antigen, AE = adverse event

This study has several limitations. First, as a retrospective analysis, the findings may be subject to variability in data quality and inconsistencies in data collection. Additionally, the short follow-up period and small sample size present significant constraints. While caution is necessary when generalizing these results, the limited availability of reports on triplet therapy makes our findings potentially valuable for clinical practice. Future large-scale, real-world studies with extended follow-up are needed to provide more robust evidence and a stronger basis for clinical decision-making in mCSPC.

In conclusion, this study highlights our initial real-world experience with triplet therapy including darolutamide for patients with mCSPC at a single academic hospital in Japan. The results demonstrated a favorable PSA response and high tolerability; however, progression patterns and subsequent therapy needs varied among patients. These findings underscore the importance of vigilant follow-up and personalized treatment strategies for patients with mCSPC receiving triplet therapy.

Availability of data and materials: The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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