The Effect of Upfront Intensive Therapy on Primary Resistance in Metastatic Castration-sensitive Prostate Cancer: A Multicenter Retrospective Study

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Research Article

Keywords: prostate cancer, castration-sensitive, castration-resistant, upfront, prognosis

Posted Date: August 6th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-711200/v1>

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Abstract

We investigated the effect of upfront intensive therapy on primary resistance in patients with metastatic castration-sensitive prostate cancer (mCSPC) in real-world practice. We retrospectively evaluated the medical records of 348 patients with newly diagnosed mCSPC who had a high tumor-burden between January 2008 and May 2021. We compared the oncological outcomes between patients who received conventional androgen deprivation therapy $\pm$ bicalutamide (ADT group) and those treated with upfront intensive therapies (upfront group). The primary purpose was comparing the rate of primary resistance between the ADT and upfront groups. The primary resistance was defined as a castration-resistant prostate cancer (CRPC) progression < 6 or < 12 months. The secondary purposes were comparing the CRPC-free survival and overall survival (OS) between the ADT and upfront groups, and assessing safety in the upfront group. We identified 206 and 142 patients for the ADT and upfront groups, respectively. We found the rate of CRPC progression < 6 and < 12 months was significantly lower in the upfront group (9.2% and 18%, respectively) than that in the ADT group (21% and 51%, respectively). The upfront therapy was significantly associated with favorable CRPC-free survival and OS than that in the ADT group in propensity-score adjusted models. A higher rate of any grade adverse events was observed in the upfront docetaxel (94%) than that of the upfront abiraterone (34%) or apalutamide/enzalutamide (39%). In conclusion, the upfront intensive therapy significantly improved the rate of primary resistance and oncological outcomes in patients with mCSPC in real-world practice.

Introduction

In Western countries and Japan, prostate cancer (PC) is the most frequent cancer in men.^{1–3} Although androgen deprivation therapy (ADT) is the standard treatment for metastatic castration-sensitive prostate cancer (mCSPC), progression to metastatic castration-resistant PC (CRPC) remains a major cause of deaths in men with cancer.^{4–8} Recent studies have shown that upfront intensive therapy, including docetaxel (DTX), abiraterone (ABI), apalutamide (APA), and enzalutamide (ENZ), has a significant benefit in treating mCSPC^{9–13} and became a standard of care for patients with mCSPC.¹⁴ However, there is a concern about the benefit–harm balance in these upfront intensive therapies because Japanese patients have relatively better responses to primary ADT plus bicalutamide (complete androgen blockade) than Westerners.¹⁵ Therefore, real-world data to prove the advantage of upfront intensive therapy over ADT plus bicalutamide in Japanese patients are awaited. We retrospectively investigated the effect of upfront intensive therapy on the rate of primary resistance, oncological outcomes, and safety in patients with mCSPC.

Results

Of the 554, we identified 348 eligible patients with high tumor burden. Of 348, 206 and 142 patients were divided in the ADT and upfront groups, respectively (Fig. 1). The median age in this cohort was 72 years. The median follow-up periods in the ADT and upfront groups were 37 (IQR, 21–58) and 22 (11–29)

months, respectively. Most patients in the ADT group were treated with CAB (n = 193, 94%). No significant difference was observed in ECOG PS, PSA, Gleason score, EOD score, and high-volume or high-risk disease between the groups (Table 1). Median time from the initial ADT to subsequent upfront intensive therapy (ADT plus DTX, ABI, APA, or ENZ) was 0.6 (IQR 0.0-1.7) months. The number of patients with the upfront DTX, ABI, APA, and ENZ were 32, 71, 25, and 14, respectively. Background of patients with upfront ARTs was shown in Table 2. In patients with upfront DTX, the median cycle of DTX administration was 6 (IQR, 6–6), whereas dose reduction was required in six cases (19%). The completion of the planned six cycles of DTX administration reached 28 cases (88%).

Table 1
Background of patients

	ADT group	Upfront Group	P value
Number of patients, n	206	142	
Age, years (IQR)	72 (65–78)	72 (68–76)	0.961
ECOG PS, n			0.113
0	155 (75%)	117 (82%)	
1	30 (15%)	15 (11%)	
>1	21 (10%)	10 (7.0%)	
PSA, ng/mL (IQR)	367 (96-1407)	347 (71-1000)	0.541
Gleason score, n			
6 or 7	12 (5.8%)	3 (2.1%)	
8	42 (20%)	43 (30%)	
9	117 (57%)	77 (54%)	
10	35 (17%)	19 (13%)	
Gleason score 9 or 10, n	152 (74%)	96 (68%)	0.165
EOD score (IQR)	2 (2–3)	2 (1–3)	
EOD score 3 or 4	91 (49%)	64 (45%)	0.869
CHAARTED high-volume	206 (100%)	138 (97%)	
LATITUDE high-risk	195 (95%)	141 (99%)	
Initial therapy, n			
ADT alone	13 (6.3%)		
ADT plus bicalutamide	193 (94%)		
ADT plus upfront Docetaxel (DTX)		32 (23%)	
ADT plus upfront abiraterone (ABI)		71 (50%)	
ADT plus upfront apalutamide (APA)		25 (18%)	
ADT plus upfront enzalutamide (ENZ)		14 (10%)	
IQR: interquartile range, ECOG PS: Eastern Cooperative Oncology Group Performance Status, ADT: androgen deprivation therapy, EOD: extent of disease			

Table 2
Background of patients with upfront ARATs

	Upfront DTX	Upfront ARATs	<i>P value</i>
Number of patients, n	32	110	
Age, years (IQR)	71 (66–76)	72 (68–77)	0.280
ECOG PS, n			0.030
0	30 (94%)	85 (77%)	
1	2 (6.3%)	15 (14%)	
>1	0 (0%)	10 (9.0%)	
PSA, ng/mL (IQR)	557 (54–1140)	342 (66–820)	0.676
Gleason score, n			
6 or 7	0 (0%)	3 (2.7%)	
8	5 (16%)	38 (35%)	
9	22 (69%)	55 (50%)	
10	5 (16%)	14 (9.9%)	
Gleason score 9 or 10, n	27 (84%)	69 (63%)	0.031
EOD score (IQR)	2 (1–3)	2 (2–3)	
EOD score 3 or 4	12 (38%)	52 (36%)	0.420
CHAARTED high-volume	32 (100%)	106 (96%)	
LATITUDE high-risk	32 (100%)	109 (99%)	
Initial therapy, n			
Upfront Docetaxel (DTX)	32 (100%)		
Upfront abiraterone (ABI)		71 (65%)	
Upfront apalutamide (APA)		25 (23%)	
Upfront enzalutamide (ENZ)		14 (13%)	
ARATs: androgen receptor-axis-targeted agents			

Primary outcomes

The rate of CRPC progression < 6 months was significantly lower in the upfront group than that in the ADT group (9.2% vs. 21%, respectively; $P = 0.004$, Fig. 2A). The rate of CRPC progression within 6 in the upfront DTX, ABI, and APA/ENZ was 9.4%, 7.1%, and 13%, respectively (Fig. 2A).

The rate of CRPC progression < 12 months was significantly lower in the upfront group than that in the ADT group (18% vs. 51%, respectively; $P < 0.001$, Fig. 2B). The rate of CRPC progression within 6 in the upfront DTX, ABI, and APA/ENZ was 16%, 18%, and 21%, respectively (Fig. 2B).

Secondary outcomes

Unadjusted CRPC-free survival was significantly longer in the upfront ARATs than that in the ADT group (median, 39 vs. 12 month) (Fig. 3A). Unadjusted OS was significantly longer in the upfront ARATs than that in the ADT group (median, undefined vs. 48 month) (Fig. 3B). IPTW-adjusted multivariable Cox regression analysis revealed that the upfront therapy was significantly associated with favorable CRPC-free survival (HR, 0.45; $P < 0.001$, Fig. 3C) and OS (HR, 0.49; $P = 0.006$, Fig. 3D). Among the upfront group, we observed higher rate of any grade and grade 3–4 AEs in the upfront DTX (93% and 59%, respectively) than those in the upfront ABI (47% and 13%, respectively) and those in the upfront APA/ENZ (39% and 5.1%, respectively) (Fig. 4A). The major AE in the upfront DTX, upfront ABI, and upfront APA/ENZ was hematotoxicity followed by gastrointestinal tract events (Fig. 4B), liver dysfunction followed by gastrointestinal tract events (Fig. 4C), and skin events (Fig. 4D), respectively. We observed a higher rate of AR-related hospitalizations in the upfront ABI (17%) than that in the upfront DTX (3.1%) and APA/ENZ (10%) (Table 3).

Table 3
Safety of the upfront group (CTCAE v5.0)

Upfront group	All	Upfront DTX	Upfront ABI	Upfront APA/ENZ
Any grade, n	64 (51%)	30 (94%)	24 (34%)	15 (39%)
Grade 3 or higher, n		19 (59%)	9 (13%)	2 (5.1%)
AE-related hospitalization, n		1 (3.1%)	7 (9.9%)	1 (2.6%)
AE-related discontinuation, n		1 (3.1%)	12 (17%)	4 (10%)
Type of AE	Grade	Number of events	Number of events	Number of events
Liver dysfunction	Grade 4		1	
	Grade 3		1	
	Grade 2		4	
	Grade 1	1	3	1
Hematotoxicity	Grade 4	2		
	Grade 3	16	1	
	Grade 2	6	1	
	Grade 1	2		
Febrile Neutropenia	Grade 3	5		
Gastrointestinal ulcer	Grade 4		1	
	Grade 3		1	
	Grade 2		1	
Appetite loss	Grade 3		1	
	Grade 1	5		
Nausea	Grade 1	1		
Constipation	Grade 3		1	
	Grade 2		1	
	Grade 1	2		1

AE: adverse event, DTX: docetaxel, ABI: abiraterone, APA: apalutamide, ENZ: enzalutamide

Upfront group	All	Upfront DTX	Upfront ABI	Upfront APA/ENZ
Diarrhea	Grade 1	1	1	
Dysgeusia	Grade 2	1		
	Grade 1	2		
Fatigue	Grade 3		2	
	Grade 2	4		
	Grade 1	3		1
Pain	Grade 2	2	1	
	Grade 1	3		
Pneumonia	Grade 3	1		
	Grade 1	1		1
Urinary tract infection	Grade 3		1	
Skin rash	Grade 3			2
	Grade 2	3	1	4
	Grade 1	2		7
Hypertension	Grade 2		1	
Edema	Grade 2	4		
	Grade 1	1		
Peripheral neuropathy	Grade 2	1		
	Grade 1	3		
Insomnia	Grade 1	1		
Hair loss	Grade 1	1		
Glucose intolerance	Grade 3		1	
Total events		74	25	17
Events/patient		2.3	0.4	0.4
AE: adverse event, DTX: docetaxel, ABI: abiraterone, APA: apalutamide, ENZ: enzalutamide				

Exploratory outcomes

Unadjusted CRPC-free survival was significantly longer in the upfront ARATs and DTX than that in the ADT group (median, undefined, 27, vs. 12 months, respectively) (Fig. 5A). Unadjusted CRPC-free survival was not significantly different between the upfront ABI and APA/ENZ groups (Fig. 5B). Unadjusted OS was significantly longer in the upfront ARATs than that in the ADT group (median, undefined, undefined, vs. 48 months) (Fig. 5C). The achievement rate of $\text{PSA} \leq 0.2 \text{ ng/mL}$ was significantly higher in the upfront group (57%) than that in the ADT group (31%) (Fig. 5D). The rate of $\text{PSA} \leq 0.2 \text{ ng/mL}$ in the upfront DTX, ABI, and APA/ENZ was 45%, 66%, and 54%, respectively.

Discussion

We compared the rate of primary resistance and oncological outcomes between the conventional ADT and upfront intensive therapies in patients with newly diagnosed mCSPC in our clinical practice. We found significantly improved CRPC progression rate < 6 or 12 months after upfront therapy than those in the conventional ADT therapy. Moreover, we observed significantly prolonged CRPC-free survival and OS in patients treated with upfront intensive therapy than those who received conventional ADT therapy. This study demonstrated the benefit of upfront intensive therapy over the ADT therapy on the oncological outcomes in real-world practice in Japan.

As radiological imaging tests were performed around 6 to 12 months in clinical practice, the main definition for CRPC progression within 6 months was the PSA progression in this study. The rate of primary resistance within 6 months in the upfront intensive therapy was approximately 3–12% in several phase III clinical trials. The time to PSA progression within the first 6 months in the upfront arm vs. control arm was approximately 3–4% vs. 14% in the STAMPEDE trial (DTX),¹⁶ 12% vs. 33% in the LATITUDE trial (ABI),¹⁰ 10% vs. 25% in the TITAN trial (APA), 5% vs. 23% in the ARCHES trial (ENZ),¹⁷ and 4% vs. 13% in the ENZAMET trial (ENZ).¹² The 9.2% of primary resistance rate in the upfront intensive therapies was comparable to landmark clinical trials (range 3–12%) and no remarkable difference was observed among the type of treatment regimens.

The selection of upfront DTX or ARATs therapy for mCSPC is debatable. As no study directory has compared the efficacy of upfront intensive therapies, indirect comparisons using network meta-analysis support the superiority of upfront ARATs therapy over upfront DTX.^{18–20} We found persistent decline of CRPC-free survival in the patients with upfront DTX therapy (Fig. 5A). Although the rate of primary resistance was similar group, treatment efficacy of upfront DTX may be not sustainable. In consideration with higher AEs rate in the upfront DTX, this regimen can be used in patients who might have neuroendocrine differentiation.²¹ As mCSPC had heterogeneous characteristics, molecular biomarkers are necessary for selecting treatment in those patients.^{22–25}

The safety profile between the upfront DTX and ARATs therapies is a key factor for treatment selection. We observed a significant difference in toxicities between the upfront DTX and ARATs groups. Although

no study directory compared the safety between upfront DTX and ARATs therapies, a recent network meta-analysis showed that the prevalence of high-grade AEs was significantly lower in patients treated with enzalutamide (OR, 0.56; 95% CI, 0.35–0.92) and apalutamide (OR, 0.44; 95% CI, 0.24–0.79) than those who received DTX.²⁰ Furthermore, ad-hoc analysis of quality of life (QOL) comparison in the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy trial reported that global QOL was significantly higher in the ABI arm compared to the DTX arm (+ 3.9; 95% CI, 0.6–7.1; $P = 0.021$). Although the results of that network meta-analysis need careful consideration, upfront ARATs therapies might have less toxicity than upfront DTX therapy. Similarly, we observed a significantly higher rate of AEs in the upfront DTX group than that in the upfront ARATs group. However, the major AE in the DTX group was non-symptomatic hematotoxicities and preventable by granulocyte colony-stimulating factor.²⁶ Caution is required for the higher rate of AE-related hospitalization and discontinuation in the upfront ABI group (9.9% and 17%, respectively) than in the upfront DTX (3.1% and 3.1%, respectively) or upfront APA/ENZ (2.6% and 10%, respectively) group. We should recognize that upfront intensive therapies can increase the risk of harmful toxicities despite their efficacy.

The retrospective study design, small sample size, selection bias, and immeasurable confounding factors limit this study. Our results may not be applied to other countries because of racial, regional, and insurance system differences. Despite these limitations, our results confirmed the potential utility of upfront intensive therapy in real-world practice. Further long-term observations are necessary to clarify the benefits of upfront therapies in patients with mCSPC.

In conclusion, upfront intensive therapies significantly improved the rate of primary resistance and oncological outcomes in patients with newly diagnosed mCSPC in real-world practice.

Patients And Methods

This retrospective study follows the ethical standards of the Declaration of Helsinki, and the ethics review board of the Hirosaki University School of Medicine approved this study (authorization number: 2019–094) and all hospitals in this study. Pursuant to the provisions of the ethics committee and the ethics guideline in Japan,²⁷ written consent was not required in exchange for public disclosure of study information (opt-out approach) in the case of retrospective and/or observational study using a material such as the existing documentation.

Study population and patient selection

We retrospectively evaluated the medical records of 554 patients with mCSPC who were treated at Hirosaki University Hospital and associated hospitals between January 2008 and March 2021. Inclusion criteria were mCSPC patients with CHAARTED high-volume or LATITUDE high-risk (high tumor burden)^{10, 13}, and who were treated with ADT alone, ADT plus bicalutamide, or upfront intensive therapy as a standard of care. Patients without insufficient baseline clinical information were excluded. Finally, 332 patients with mCSPC who had high tumor burden were enrolled (Fig. 1). Patients were divided into two

groups: those treated with ADT alone or ADT plus bicalutamide (ADT group) and those who received upfront intensive therapy (upfront group) such as upfront DTX, upfront abiraterone (ABI), upfront apalutamide (APA) or upfront enzalutamide (ENZ).

Variable evaluations

The following variables were investigated at diagnosis: age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), Gleason score, serum PSA, time to CRPC diagnosis, PSA nadir, CRPC-free survival, and OS. Metastatic status was evaluated via chest and body computed tomography and bone scintigraphy before initiating ADT. Bone metastatic volume was evaluated using the extent of disease (EOD) score on bone scintigraphy. CRPC-free survival was evaluated from the date of the initial diagnosis of mCSPC to the date of CRPC diagnosis following the recommendations of the Cancer Clinical Trials Working Group 2²⁸. OS were evaluated from the date of the initial diagnosis of mCSPC to the date of any cause of death or final follow-up.

Treatment protocol

Treatment was selected based on the decision of the attending physicians. Patients were initially treated with ADT alone or ADT plus bicalutamide before the approval of upfront intensive therapy. After June 2016, we started providing upfront intensive therapy in patients with high tumor burden. After the diagnosis of CRPC, patients underwent sequential therapy including taxane-based chemotherapy or second-generation androgen receptor-axis-targeted agents (ARATs) such as ABI, APA, or ENZ.

Primary purposes

The comparison of the rate of primary resistance between the ADT and upfront groups. The primary resistance was defined as a PSA progression, radiologic progression, or any cause of death within 6 or 12 months.

Secondary purposes

The comparison of CRPC-free survival and OS between the ADT and upfront groups, and assessing safety in the upfront group. Adverse events (AEs) were evaluated using the Common Terminology Criteria for Adverse Events version 5.0.

Exploratory purposes

The exploratory purposes were to compare the CRPC-free survival and OS between the ADT group and patients treated with upfront DTX, and between the ADT group and patients treated with upfront ARATs (ABI/APA/ENZ). The achievement rate of PSA $\leq$ 0.2 ng/mL was also evaluated.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 7.00 (GraphPad Software, San Diego, CA, USA), BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and R 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). Fisher's exact test, chi-squared test, Student's t-

test, or Mann–Whitney U-test was used to compare the statistical difference between the groups. OS was estimated and compared using the Kaplan–Meier curve and log-rank test, respectively. Multivariable Cox regression analysis was conducted to investigate the effect of upfront intensive therapy after adjusting for potential confounders using a propensity score-based inverse probability of treatment weighting (IPTW) method to adjust for group imbalances in the oncological outcomes.^{29,30} HRs with 95% CIs were calculated after controlling for potential confounders for upfront therapy, including patient age, ECOG PS, Gleason score, EOD. *P* values < 0.05 were considered statistically significant.

Declarations

Acknowledgments

The authors would like to thank Akiko Okamoto, Itsuto Hamano, Yuta Kojima, Yuka Kubota, Masaki Momota, Teppei Matsumoto, Ayumu Kusaka, Masaaki Oikawa, Naoki Fujita, Hiromichi Iwamura, Yuichiro Suzuki, Naoki Sugiyama, Satoshi Narita, Shoji Nishimura, Kazuaki Yoshikawa, Shinya Takahashi, Toshiaki Kawaguchi, Hiroyuki Ito, Tadafumi Saito, Atsushi Sasaki, Hisao Saitoh, Yuki Fujita, Yukie Nishizawa, Satomi Sakamoto, and Tohru Yoneyama for their invaluable support. The authors would like to thank Eiki Tsushima for R commander modification for IPTW analysis.

Funding

This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Numbers 21K09364 (Yasuhiro Hashimoto), 20K18083 (Hirotake Kodama), 19H05556 (Chikara Ohyama), 20K09517 (Shingo Hatakeyama), and 20K18130 (Takuma Narita).

Data availability statement:

The minimal data set of the present study is available on request.

Code Availability:

none

Authors' Contribution:

All authors reviewed the manuscript.

T. Tanaka: Data collection

S. Hatakeyama: Project development, manuscript writing, data analysis, data collection

D. Noro: Data collection

H. Kodama: Data collection

S. Konishi: Data collection

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C. Ohyama: Data collection, critical review

Ethics Approval:

This multicenter retrospective study was performed according to the ethical standards of the Declaration of Helsinki and was approved by the ethics review boards of the Hirosaki University School of Medicine (authorization number: 2019–094) and all hospitals.

Informed consent:

Pursuant to the provisions of the ethics committee and the ethics guideline in Japan, written consent was not required in exchange for public disclosure of study information (opt-out approach) in the case of retrospective and/or observational study using a material such as the existing documentation.

Consent to Participate:

Written consent was not obtained in exchange for the public disclosure of study information (opt-out approach).

Consent for Publication:

All authors approved for the publication.

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Figures

Fig. 1

Figure 1

Patient selection. Patients with high tumor burden (CHAARTED high-volume or LATITUDE high-risk) were selected in this study. Finally, we identified 206 and 126 patients in the ADT and upfront groups, respectively.

Fig. 2

Figure 2

Primary outcomes. The comparison of the rate of primary resistance (CRPC progression < 6 months) between the ADT and upfront groups (A). The comparison of the rate of primary resistance (CRPC progression < 12 months) between the ADT and upfront groups (B). DTX: docetaxel, ABI: abiraterone, APA: apalutamide, ENZ: enzalutamide

Fig. 3

Figure 3

Secondary outcomes Unadjusted CRPC-free survival comparison between the ADT and upfront groups (A). Unadjusted OS comparison between the ADT and upfront groups (B). Multivariable Cox regression analysis using a propensity score-based inverse probability of treatment weighting (IPTW) method for CRPC-free survival after adjusting for potential confounders (age, ECOG PS, Gleason score, and EOD score for the upfront intensive therapy) (C). IPTW-adjusted multivariable Cox regression analysis for OS (D).

Fig. 4

Figure 4

Safety profile Safety profile of upfront intensive therapies was shown using CTCAE v5.0 (A). Detailed adverse events (AEs) in the upfront DTX therapy (B), in the upfront ABI therapy (C), and in the upfront APA/ENZ therapy (D) were shown.

Fig. 5

Figure 5

exploratory outcomes of CRPC-free survival and OS. Comparison of the CRPC-free survival between the ADT, upfront ARATs, and upfront DTX(A). Comparison of the CRPC-free survival between the upfront ABI and upfront APA/ENZ (B). Comparison of the OS between the ADT, upfront ARATs, and upfront DTX(C). Comparison of the achievement rate of PSA ≤ 0.2 ng/mL (D).

Supplementary Files

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