Effect of apalutamide dosage on the incidence of cutaneous adverse events and prostate-specific antigen reduction in patients with prostate cancer

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Abstract. Apalutamide (Erleada®; Janssen-Cilag Ltd.; Johnson & Johnson) is an effective therapeutic agent for prostate cancer; however, adverse events, particularly cutaneous toxicity, may lead to treatment discontinuation. Among Japanese patients, the incidence of cutaneous toxicity is relatively high and increased drug exposure has been reported in individuals with a small body size. In the present retrospective study, the effects of a reduced dose of apalutamide with stepwise escalation on the incidence of cutaneous toxicity and treatment efficacy were evaluated. Patients with prostate cancer who received apalutamide at Ogaki Municipal Hospital (Ogaki, Japan) between May 2019 and September 2024 were included in the present study. Based on their initial dose, patients were categorized into the standard-dose (240 mg; n=26) or reduced-dose (120 or 180 mg; n=20) group. The incidence and severity of cutaneous toxicity, time to the first cutaneous event and time to achieve prostate-specific antigen (PSA) <0.2 ng/ml and progression-free survival (PFS) were compared. Cutaneous toxicity occurred in 73.1 and 40.0% of the standard-dose and reduced-dose groups, respectively (P=0.036). Grade ≥3 toxicity was observed only in the standard-dose group (11.5%). The median time to the first cutaneous event was 63.0 vs. 45.5 days (P=0.193). The median time to achieve PSA <0.2 ng/ml was 120.0 days in both groups (P=0.822). The median PFS was not reached in the standard-dose group but was 693 days in the reduced-dose group (P=0.116). Overall, initiating apalutamide at a reduced dose with gradual escalation may mitigate the risk of cutaneous toxicity without compromising the PSA response. These findings provide clinically relevant insights, particularly for patients with a small body size, however further demonstration in larger prospective studies is warranted.

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Abbreviations: BSA, body surface area; PSA, prostate-specific antigen; RDI, relative dose intensity; PFS, progression-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer

Key words: apalutamide, prostate cancer, cutaneous toxicity, dose reduction

Introduction

Prostate cancer is one of the most prevalent malignancies in men, with an estimated 1.47 million new cases worldwide in 2022, and its incidence continues to increase annually, particularly in the aging population (1). Apalutamide, an androgen receptor inhibitor, which is indicated for both non-metastatic castration-resistant prostate cancer (nmCRPC) and metastatic castration-sensitive prostate cancer (mCSPC) is widely used as a standard therapeutic option (2-4).

While apalutamide demonstrates notable clinical efficacy, including a marked reduction in prostate-specific antigen (PSA) levels and prolonged time to metastasis, adverse events such as cutaneous toxicities (including rashes and pruritus) have been reported, potentially compromising the quality of life and treatment adherence (3-5). Rashes associated with apalutamide have been documented in 15.3-21.8% of patients, underscoring the necessity of its management (3,4). In addition, a notably high incidence of rashes (51.5%) has been reported in Japanese patients, highlighting the need for vigilance in this specific population (5). Low body weight may be associated with increased systemic exposure to apalutamide (6). Sasaki *et al* (7) reported a markedly high incidence of cutaneous adverse events in patients weighing <67 kg and with a BMI <24 kg/m^2. Furthermore, Katsuta *et al* (8) demonstrated a markedly higher incidence of rashes in patients with a low body weight. However, additional studies have reported no notable association between body size and rash occurrence (5,9), exhibiting how findings across these studies are inconsistent.

Therefore, a reduced initial dose of apalutamide may be used in real-world clinical practice to mitigate the risk of severe adverse events. Oishi *et al* (10) compared the safety and efficacy of standard and reduced doses of apalutamide and

found no notable differences between the groups. However, this analysis was limited to fixed-dose regimens at treatment initiation and did not evaluate the dynamic strategies for dose adjustment. To the best of our knowledge, to date, no studies have investigated the 'reduced-dose initiation with stepwise escalation' approach, which may provide clinically relevant insight into the safety and efficacy of flexible dosing strategies tailored to individual patient characteristics. Although the standard daily dose of apalutamide is 240 mg (1), the association between dosage, adverse events and therapeutic efficacy remains unclear.

Among surrogate measures used to assess treatment efficacy, PSA kinetics, particularly PSA <0.2 ng/ml, are regarded as indicators of a favorable treatment response. Furthermore, the time required to reach this threshold reflects the speed of response and has been suggested to correlate with prognosis (11).

Subsequently, the present retrospective study focused on the clinical impact of initiating apalutamide at a reduced dose, followed by gradual escalation, to reduce the risk of adverse events. Specifically, the effect of apalutamide dosage on the incidence of cutaneous toxicities and PSA dynamics was examined, with a particular emphasis on the time to achieve PSA <0.2 ng/ml, as well as progression-free survival (PFS) between the standard-dose and reduced-dose groups.

Materials and methods

Patients. A total of 46 patients who were newly prescribed apalutamide at Ogaki Municipal Hospital (Ogaki, Japan) between May 2019 and September 2024, were included in the present study. All 46 patients were followed until treatment discontinuation or the determined data cutoff date (March 2025), depending on whichever occurred first. Prior to the analysis, predefined exclusion criteria that were set to evaluate participants eligibility based on treatment tolerability and outcomes included: i) Patients who did not continue apalutamide beyond their first prescription; ii) patients who transferred to another institution during the treatment period, making adequate follow-up impossible; and iii) patients deemed unsuitable due to severe comorbidity, poor performance status or other conditions that precluded adequate assessment of treatment outcomes.

Study methods. Patients were stratified into two groups according to the initial prescribed dose of apalutamide, namely the standard-dose (240 mg; n=26) and reduced-dose (120 mg; n=8 or 180 mg; n=12) groups. According to the Japanese package insert, the standard approved dose of apalutamide is 240 mg once daily, with stepwise dose reductions to 180 and 120 mg if necessary (2). The initial and subsequent dose adjustments were determined at the discretion of the treating physicians, based on the clinical characteristics of each patient, including age, comorbidities, performance status and tolerance to prior androgen receptor pathway inhibitors. No predefined institutional criteria for dose selection, escalation or reduction were established. In clinical practice, dose reductions from the standard 240 mg/day to 180 or 120 mg/day were implemented stepwise according to the emergence and severity of adverse events, graded using the Common Terminology Criteria for Adverse Events (version 5.0) (12), together with physician judgment.

Statistical analysis. Between the two groups, the relative dose intensity (RDI), incidence and severity of adverse events (with a particular focus on cutaneous toxicities), time to the first occurrence of cutaneous toxicity after apalutamide initiation and treatment discontinuation owing to cutaneous toxicity, were compared. As efficacy endpoints, the time to achieve PSA <0.2 ng/ml and PFS were evaluated. The RDI was calculated as the total number of tablets prescribed from treatment initiation to the end of treatment, divided by the planned standard dose (four tablets of apalutamide at 60 mg per day) and further divided by the total number of treatment days, including treatment interruptions. Patient characteristics were compared using Mann-Whitney U tests and the χ^2 test or Fisher's exact test, as appropriate. The incidence and severity of adverse events, management of the first occurrence of cutaneous toxicity and reasons for treatment discontinuation in the two groups were compared using Mann-Whitney U tests and the χ^2 test or Fisher's exact test, as appropriate. Differences in the time to achieve PSA <0.2 ng/ml and PFS between the two groups were analyzed using log-rank tests. $P<0.05$ was considered to indicate a statistically significant difference. EZR software (version 1.61; Division of Hematology, Saitama Medical Center, Jichi Medical University) was used for all analyses (13).

Results

Patient characteristics. No patients initiated on apalutamide during the present study period fulfilled the predefined exclusion criteria, hence no patients required exclusion. The patient characteristics are summarized in Table I. The median age of those in the standard-dose group was 73 (range, 48-87) years while that for those in the reduced-dose group was 78 (range, 58-90) years (P=0.156). The median body surface area (BSA) was 1.73 m^2 (range, 1.48-1.92) in the standard-dose group and 1.60 m^2 (range, 1.29-1.86) in the reduced-dose group (P=0.049). The number of patients with mCSPC was 21/26 in the standard-dose group and 13/20 in the reduced-dose group (P=0.385). The median RDIs were 97.2 and 59.3% in the standard- and reduced-dose groups, respectively (P<0.001). Dose escalation during treatment was observed in 7 patients in the reduced-dose group (P=0.001), whereas dose reductions occurred in 7 patients in the standard-dose group and 6 patients in the reduced-dose group (P>0.999). The median observation period was 336.0 days (range: 18.0-1,540.0) in the standard-dose group and 180.5 days (range, 14.0-1,405.0) in the reduced-dose group, with no significant difference found between the groups (P=0.103; data not shown).

Incidence of adverse events. Results of the incidence and severity of adverse events analysis are presented in Table II. Adverse events occurred in 76.9% (20/26) and 65.0% (13/20) of patients in the standard-dose and reduced-dose groups, respectively (P=0.575). The incidence of cutaneous toxicities (all grades) was 73.1% (19/26) in the standard-dose group and 40.0% (8/20) in the reduced-dose group (P=0.036).

Table I. Patient characteristics of the standard-dose group and reduced dose-group.

Characteristic	Standard-dose group (n=26)	Reduced-dose group (n=20)	P-value
Age, years	73 (48-87)	78 (58-90)	0.156
Weight, kg	63.7 (45.4-78.7)	58.8 (37.9-73.0)	0.064
≥67	10	5	
<67	16	15	
BMI, kg/m^2	23.4 (17.6-27.5)	22.4 (16.2-26.8)	0.394
≥24	9	4	
<24	17	16	
BSA, m^2	1.73 (1.48-1.92)	1.60 (1.29-1.86)	0.049
Indication			0.385
mCSPC	21	13	
nmCRPC	5	7	
Initial PSA, ng/ml			
mCSPC	20.33 (0.41-968.13)	12.36 (0.50-33.69)	0.576
nmCRPC	3.16 (0.44-4.88)	11.55 (1.27-28.85)	0.030
RDI, %	97.20 (23.53-100.00)	59.30 (5.60-95.50)	<0.001
Dose adjustment	7	13	0.016
Escalation	0	7	0.001
Reduction	7	6	>0.999

P-values were calculated using the χ^2 test for indication (mCSPC vs. nmCRPC) and dose adjustment, Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Values are presented as the median (minimum-maximum) or no. of patients. BSA, body surface area; mCSPC, metastatic castration-sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; RDI, relative dose intensity.

No grade ≥3 cutaneous toxicities were observed in the reduced-dose group.

Time to the first occurrence of cutaneous toxicity and management. Management at the first occurrence of cutaneous toxicity is summarized in Table III. The median time to the first cutaneous event was 63.0 (range, 14.0-142.0) days in the standard-dose group and 45.5 (range, 15.0-81.0) days in the reduced-dose group (P=0.193). Furthermore, there were no significant differences between the two groups in the management approaches at the first occurrence of cutaneous toxicity (all P>0.05).

Reasons for treatment discontinuation. Reasons for treatment discontinuation are summarized in Table IV. The discontinuation rate owing to cutaneous toxicity was 19.2% (5/26) in the standard- and 15.0% (3/20) in the reduced-dose group (P>0.999).

Dose modifications. Details of the dose modifications are presented in Table V. Among the 20 patients in the reduced-dose group, 7 patients remained on the initial dose, 6 patients underwent further dose reductions and 7 patients experienced dose escalation. The reasons for the additional dose reduction included patient preference (n=1), rash (n=4) and neutropenia (n=1). Among the 26 patients in the standard-dose group, 19 were maintained on their initial dose, while 7 patients required dose reduction, all due to a rash. The clinical course and dose-escalation timeline in patients who commenced apalutamide at a reduced dose are summarized in Table VI. Notably, one patient (patient no. 1) was initiated at 120 mg/day, escalated to 180 mg/day on day 29 and 240 mg/day on day 57, without the occurrence of cutaneous toxicity during this period. However, cutaneous toxicity developed on day 92, leading to a dose reduction to 120 mg/day. As cutaneous symptoms did not adequately improve, treatment was discontinued on day 97. An additional patient (patient no. 2) who was also initiated at 120 mg/day, temporarily discontinued treatment on day 76 due to cutaneous toxicity, but resumed therapy at 120 mg/day on day 148, after symptoms improved. The dose was then escalated to 180 mg/day on day 442 and the patient continued treatment until disease progression. No cutaneous toxicity was observed in the remaining 5 patients either before or after dose escalation.

Time to achieve PSA <0.2 ng/ml and PFS. Details of the time taken to achieve PSA <0.2 ng/ml are shown in Fig. 1. The median time was 120.0 (95% CI, 60.0-not reached) days in both the standard-dose and reduced-dose groups (P=0.822; Fig. 1). PFS is shown in Fig. 2. The median PFS was not reached in the standard-dose group (95% CI, 783.0 days-not reached) and 693.0 (95% CI, 328.0-not reached) days in the reduced-dose group, with no significant difference between the groups (P=0.116). Receiver operating characteristic curve analysis of the RDI/BSA for predicting cutaneous toxicity identified a cut-off value of 42.940, with an area under the curve of 0.584, sensitivity of 0.481 and a specificity of 0.737 (Fig. S1).

Table II. Incidence and severity of adverse events in the standard- and reduced dose-group.

Adverse event type	Standard-dose group (n=26), n (%)	Reduced-dose group, (n=20), n (%)	P-value
Any adverse event			
All grade	20 (76.9)	13 (65.0)	0.575
Grade ≥3	5 (19.2)	1 (5.0)	0.212
Cutaneous adverse events[a]			
All grade	19 (73.1)[a]	8 (40.0)[a]	0.036
Grade ≥3	3 (11.5)	0 (0.0)	0.246
Fatigue			
All grade	2 (7.7)[a]	2 (10.0)	>0.999
Grade ≥3	0 (0.0)	0 (0.0)	>0.999
Pneumonia			
All grade	2 (7.7)[a]	0 (0.0)	0.498
Grade ≥3	2 (7.7)	0 (0.0)	0.498
Somnolence			
All grade	1 (3.8)[a]	1 (5.0)	>0.999
Grade ≥3	0 (0.0)	0 (0.0)	>0.999
Neutropenia			
All grade	0 (0.0)	1 (5.0)	0.435
Grade ≥3	0 (0.0)	1 (5.0)	0.435
Edema of the extremities			
All grade	0 (0.0)	1 (5.0)[a]	0.435
Grade ≥3	0 (0.0)	0 (0.0)	>0.999
Fever			
All grade	0 (0.0)	1 (5.0)	0.435
Grade ≥3	0 (0.0)	0 (0.0)	>0.999

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 5.0). Cutaneous adverse events included maculopapular rash, erythema multiforme, eczema and pruritus. [a]Overlapping adverse events in individual patients.

Table III. Management at first occurrence of cutaneous toxicities in the standard- and reduced-dose group.

Item	Standard-dose (n=19)	Reduced-dose group (n=8)	P-value
Time to initial onset of cutaneous adverse events, days	63.0 (14-142)	45.5 (15-81)	0.193
Prescription of oral antihistamines	17 (89.5)[a]	5 (62.5)[a]	0.136
Single agent	14 (73.7)	4 (50.0)	0.375
Two or more agents	3 (15.8)	1 (12.5)	1.000
Treatment interruption	8 (42.1)[a]	6 (75.0)[a]	0.209
Dose reduction with continuation of therapy	1 (5.3)	0 (0.0)	>0.999
Prescription of topical agents			
Corticosteroids	14 (73.7)[a]	6 (75.0)[a]	>0.999
Moisturizers	8 (42.1)[a]	5 (62.5)[a]	0.420
Other	2 (10.5)[a]	0 (0.0)	>0.999
Prescription of oral agents			
Corticosteroids	1 (5.3)[a]	0 (0.0)	>0.999
Minocycline	1 (5.3)[a]	0 (0.0)	>0.999

Values are presented as medians (minimum-maximum) or n (%) of patients. Management strategies were recorded at the first occurrence of cutaneous adverse events, including maculopapular rash, erythema multiforme, eczema and pruritus. [a]A total of >1 management approach at the first occurrence).

Table IV. Reasons for treatment discontinuation in the standard-dose group and reduced-dose group.

Reason	Standard-dose group (n=26)	Reduced-dose group (n=20)	P-value
Adverse events (%)	7 (26.9)	5 (25.0)	>0.999
Cutaneous adverse events	5 (19.2)	3 (15.0)	>0.999
Pneumonitis	2 (7.7)	0 (0.0)	0.498
Somnolence	0 (0.0)	1 (5.0)	0.435
Pyrexia	0 (0.0)	1 (5.0)	0.435
Disease progression	6 (23.1)	6 (30.0)	0.848
Change in treatment strategy	3 (11.5)	0 (0.0)	0.246
Observation without active treatment	2 (7.7)	0 (0)	0.498
Surgery	1 (3.8)	0 (0.0)	>0.999
Details unknown	0 (0.0)	2 (10.0)	0.184
Ongoing	10 (38.5)	7 (35.0)	>0.999

Data are presented as n (%). The reasons for treatment discontinuation were determined based on physician records. Cutaneous adverse events included maculopapular rash, erythema multiforme, eczema and pruritus.

Table V. Dose modifications during treatment.

Group	Dose modification type	Dose pathway	No. of cases with body weight <67 kg and BMI <24 kg/m^2	Reason for dose reduction	No. of cases
Reduced-dose (180 mg, n=12; 120 mg, n=8)	Dose escalation	180-240 mg (n=4)	3	-	-
		120-180 mg (n=2)	1	-	-
		120-180-240 mg (n=1)	1	-	-
	Same dose	180 mg (n=4)	3	-	-
		120 mg (n=3)	2	-	-
	Dose reduction	180-120 mg (n=4)	3	Patient preference	1
				Skin rash	
				Grade 2	4
		120-60 mg (n=2)	1	Neutropenia	
				Grade 3	1
Standard-dose group (240 mg, n=26)	Same dose	240 mg (n=19)	10	-	-
	Dose reduction	240-180 mg (n=7)	5	Skin rash	
				Grade 2	4
				Grade 3	3

Dose modifications summarized for each treatment group. Values are shown as the no. of cases, with reasons for dose adjustment specified as applicable.

Discussion

To the best of our knowledge, the present study is the first retrospective report to reveal the effect of initiating apalutamide at a reduced dose with subsequent stepwise escalation on the incidence of cutaneous toxicities and PSA decline (a surrogate marker of treatment efficacy). Overall, the incidence of cutaneous adverse events was significantly lower in the reduced-dose group (40.0%) compared with the standard-dose group (73.1%) and no grade ≥3 events were observed in the reduced-dose group. There was no significant difference in the rate of treatment discontinuation due to rash between the two groups. Therefore, initiating treatment at a reduced dose may help prevent severe cutaneous toxicities, thereby minimizing treatment interruptions and enabling patients to maintain continuous therapy without compromising efficacy. By contrast, the median time to achieve PSA <0.2 ng/ml, an indicator of therapeutic response, was 120.0 days in both groups, with no significant difference between the groups. Similarly, the median PFS was not reached in the standard-dose group but was 693.0 days in the reduced-dose group, with no significant difference between the two groups. Thus, initiating treatment at a reduced dose with gradual escalation significantly decreased the incidence of cutaneous toxicities without

Table VI. Clinical course and dose-escalation timeline in patients who started apalutamide at a reduced dose.

Patient no.	Body weight, kg	BMI, kg/m^2	Day from initiation	Event
1	59.7	23.0	1	Started apalutamide at 120 mg/day
			29	Increased to 180 mg/day
			57	Increased to 240 mg/day
			92	Dose reduced to 120 mg/day due to cutaneous toxicity
			97	Treatment discontinued due to persistent cutaneous toxicity
2	73.0	24.7	1	Started at 120 mg/day
			76	Treatment interrupted due to cutaneous toxicity
			148	Restarted at 120 mg/day after cutaneous toxicity improvement
			442	Increased to 180 mg/day
			469	Discontinued due to PD
3	61.6	22.8	1	Started at 180 mg/day
			127	Increased to 240 mg/day
			694	Discontinued due to PD
4	37.9	16.2	1	Started at 120 mg/day
			127	Increased to 180 mg/day
			183	Discontinued due to PD
5	55.1	20.6	1	Started at 180 mg/day
			57	Increased to 240 mg/day (ongoing treatment)
6	67.9	22.4	1	Started at 180 mg/day
			36	Increased to 240 mg/day (ongoing treatment)
7	60.3	22.7	1	Started at 180 mg/day
			43	Increased to 240 mg/day (ongoing treatment)

Patients who initially started apalutamide at a reduced dose (120 or 180 mg/day) and subsequently underwent dose escalation are shown. Day from initiation' indicates the number of days from the start of apalutamide treatment. PD, progressive disease.

causing a marked delay in the PSA response or a reduction in treatment efficacy. However, the possibility of clinically relevant differences being overlooked cannot be excluded due to the limited sample size and number of events in the present study, yet the present findings suggest that flexible dosing strategies may mitigate adverse events without compromising efficacy, underscoring the importance of individualized treatment approaches.

In current Japanese clinical practice guidelines for prostate cancer, dose-adjustment strategies specific to apalutamide are not described (14). The approved apalutamide dosage is uniformly 240 mg once daily and recommendations for dose reduction or re-escalation in response to adverse events rely primarily on the Japanese package insert (2). Stepwise dose reductions to 180 and 120 mg are permitted based on tolerability (2). However, no further guidance is provided regarding individualized dose initiation based on patient characteristics such as body size. Consequently, in the present study, the dosing strategy used was guided by the package insert and real-world clinical considerations rather than by guideline-based recommendations.

In the reduced-dose group, the BSA at treatment initiation was significantly smaller compared with that of the standard-dose group. Previous studies have shown that patients with low body weight or small BSA are at a higher risk of increased drug exposure and cutaneous adverse events compared with those without (7,8). Therefore, the prescribing physicians may have selected reduced-dose at initiation for smaller-bodied patients to prevent excessive drug exposure. Furthermore, the incidence of cutaneous toxicity was significantly lower in the reduced-dose group compared with that in the standard-dose group and no severe cutaneous toxicities were observed. These findings indicate that the lower incidence of cutaneous toxicity in the reduced-dose group may have been attributable to the dose reduction in patients with a small BSA. While studies have reported a significant association between body size and the risk of cutaneous toxicity (7,8), other investigations have found no such relationship (5,9). A number of factors may account for these inconsistencies. First, differences in patient characteristics, including baseline disease severity, prior systemic therapy and ethnic composition, may influence rash susceptibility independent of body size. Second, variation in dosing practices, including the timing and criteria for dose escalation or reduction, could alter drug exposure and affect the incidence of rash. Third, methodological differences, including retrospective design, small sample sizes and inconsistent definitions or grading of cutaneous events, may contribute to divergent findings. Together, these factors may explain why numerous studies fail to detect a clear association between body size and rash risk. Accordingly, the present findings of a lower incidence of rash with reduced-dose initiation in a cohort with smaller body size

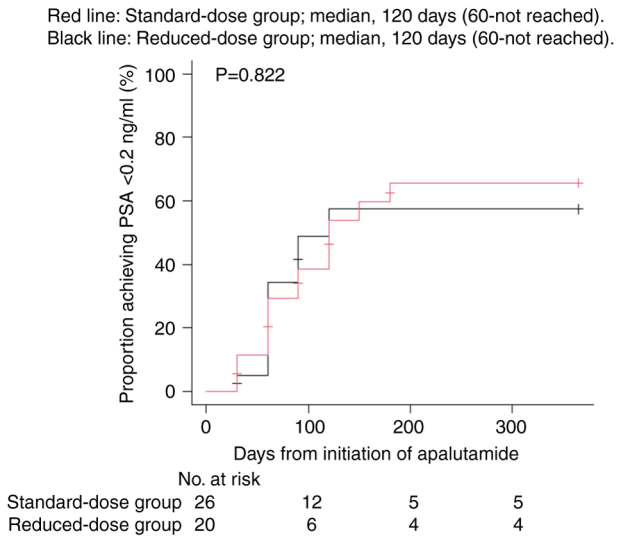

Figure 1. Time to achieve PSA <0.2 ng/ml in the standard- and reduced-dose groups. Kaplan-Meier curves showing the cumulative incidence of achieving PSA <0.2 ng/ml after apalutamide initiation. The red line represents the standard-dose group (median, 120 days; 95% CI, 60-not reached) and the black line represents the reduced-dose group (median, 120 days; 95% CI, 60-not reached). No significant difference was observed between the two groups (log-rank test, P=0.822). Number of patients at risk at each time point (0, 100, 200 and 300 days) are shown below the graph. PSA, prostate-specific antigen.

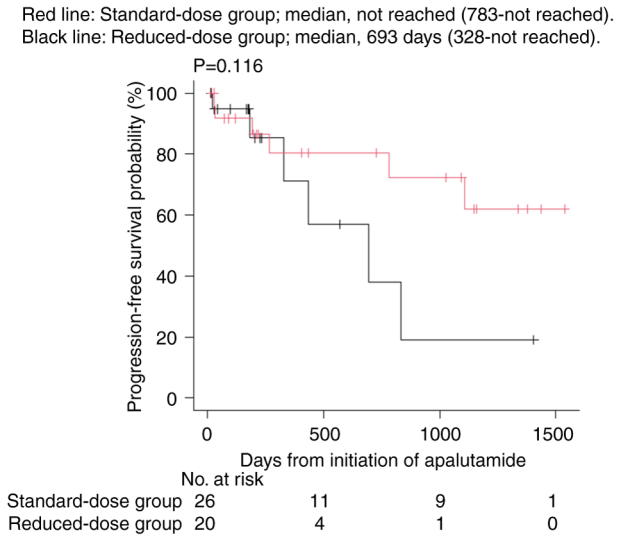

Figure 2. Kaplan-Meier curves for progression-free survival according to initial apalutamide dose. The red line indicates the standard-dose group (median, not reached; 95% CI, 783.0 days-not reached) and the black line indicates the reduced-dose group (median, 693.0 days; 95% CI, 328.0-not reached). No significant difference was observed between the two groups (log-rank test, P=0.116).

should be interpreted in light of these complexities and the limitations of real-world data. Among the seven patients in the reduced-dose group who underwent dose escalation, only 1 developed cutaneous toxicity after escalation. In this patient, the dose was increased within the first month of treatment, a rash developed on day 92 and therapy was subsequently discontinued. In the remaining 6 patients, no new adverse events were observed following dose escalation, suggesting that an initial dose reduction followed by gradual escalation after confirming tolerability may represent a safe and effective treatment strategy. These findings highlight the importance of avoiding early dose escalation and closely monitoring adverse events during the first 2-3 months of treatment.

In the standard-dose group, >50% of the patients weighed <67 kg or had a BMI <24 kg/m^2, with these populations having been previously reported to be at an increased risk of cutaneous toxicity (7). It is conceivable that the reduced initial dose in these patients may have prevented the occurrence of rash. The overall incidence of cutaneous toxicity in the present study of 58.7% (27/46) was slightly higher compared with the 51.5% reported in an integrated analysis of Japanese clinical trials (5). Similarly, in other Asian populations, the incidence of cutaneous adverse events was reported to be 32.0% in Chinese patients and 36.4% in Korean patients (15,16). This discrepancy between the present study and previous reports may be explained by the inclusion of patients with small BSA in the standard-dose group, who did not receive a dose reduction at initiation. The incidence and severity of cutaneous toxicities were significantly higher in the standard-dose group compared with the reduced-dose group and although some patients developed severe events, there was no significant difference in treatment discontinuation rates between the groups. This finding suggests that early recognition of rash and appropriate management, including temporary interruption, dose reduction and supportive care, enabled patients to continue therapy despite experiencing adverse events. Conversely, initiating apalutamide at a reduced dose may further reduce the risk of severe cutaneous toxicities and minimize the need for treatment interruption or additional interventions, representing a more practical approach in real-world clinical practice. Therefore, although treatment continuation was achievable in both groups, initiating therapy at a reduced dose may offer advantages in improving tolerability and ensuring treatment safety.

The median time to the first occurrence of cutaneous toxicity was 63.0 days in the standard-dose group and 45.5 days in the reduced-dose group, which is consistent with previous reports of a median onset of 66.0 days in Japanese patients (5). Comparable findings have been reported in other Asian populations, with a median onset of 57.5 days in Chinese and 65.5 days in Korean patients (15,16). In the TITAN trial, the median time to the first rash was 80.5 days in the overall population, compared with that of the Japanese subpopulation at 60.0 days, suggesting that patients with smaller body size may develop rashes earlier (4). Although the difference was not significant in the present study, the slightly earlier onset of cutaneous toxicity observed in the reduced-dose group may reflect the higher proportion of patients with smaller BSA in this group, consistent with the findings of the TITAN trial. This observation emphasizes the importance of early patient education and prompt management of adverse events, particularly during the initial phase of treatment in Japanese patients with smaller body size. The management of rashes at the first occurrence did not differ between the two groups with the majority of patients receiving oral antihistamines and topical corticosteroids. This finding is consistent with a previous report indicating that 71.4% of Japanese patients who developed apalutamide-related rash were treated with antihistamines (5).

Although the median RDI was significantly lower in the reduced-dose group than in the standard-dose group (59.3 vs. 97.2%), the time to achieve PSA <0.2 ng/ml and PFS did not differ significantly between the groups. This suggests a plateau effect of apalutamide, whereby the therapeutic efficacy may not increase proportionally beyond a certain drug exposure threshold (17). Interindividual variability in the PSA response, influenced by body size, drug metabolism and tumor biology, may also account for the observed findings (6,7). Considering that PSA is the only surrogate marker of treatment efficacy, short-term PSA kinetics may not fully capture overall therapeutic benefits. In the present study, no significant difference in PFS was observed between the standard-dose and reduced-dose groups. This finding is consistent with a previous report on patients with mCSPC, which demonstrated no notable difference in castration-resistant prostate cancer-free survival between standard- and reduced-dose groups (10). However, both groups in the present study included patients with nmCRPC. Conversely, another previous study suggested that initiating apalutamide at a reduced dose may reduce the time to castration-resistant prostate cancer compared with that of standard-dose initiation (18). A number of factors may explain the differing results between the previous study and the present analysis. First, the prior study only included patients with mCSPC, whereas the present cohort comprised patients with both mCSPC and nmCRPC, creating different baseline risk profiles. Second, the reduced-dose group in the previous study may have included patients who were clinically frail or those with adverse prognostic features, introducing confounding by indication. Third, variations in dose-escalation strategies, namely fixed reduced-dose initiation in the previous study vs. the flexible stepwise-escalation approach used in the present study, may have influenced the overall drug exposure and therapeutic outcomes. Given these considerations and the limited sample size of the present study, findings should be interpreted with caution. Prospective studies are further needed to determine whether reduced-dose initiation can reliably maintain oncologic outcomes across diverse patient populations. Collectively, the initial reduced dose may mitigate adverse events without compromising efficacy, however patient-specific characteristics must be considered when tailoring dosing regimens. Sasaki *et al* (7) reported that patients weighing <67 kg and with a BMI <24 kg/m^2 had a markedly higher incidence of rash, supporting the clinical relevance of body size-based dose adjustments. However, these criteria remain provisional and further research is required to establish evidence-based dosing algorithms that integrate multiple patient factors.

With regard to the time taken to achieve PSA <0.2 ng/ml and PFS, the limited sample size and number of events in the present study may have reduced the statistical power to detect modest differences. Therefore, although no significant differences were observed, the possibility of a type II error cannot be excluded. However, the similarity in the PSA response patterns between the groups suggests that reduced-dose initiation may preserve short-term antitumor efficacy, which is clinically important.

Akagi *et al* (19) reported a stronger association of rash risk with RDI adjusted for BSA compared with RDI adjusted for body weight. While this analysis focused on toxicity, the effects of RDI or RDI/BSA on the PSA response remain unexplored. To the best of our knowledge, to date, no studies have directly examined the association between RDI and PSA decline; however, previous reports have suggested that dose adjustments aimed at reducing cutaneous toxicity do not markedly affect PFS (10,17) and the present findings were consistent with these observations. Exploratory analysis identified an RDI/BSA cut-off value of 42.940 (area under the curve=0.5838: 95% CI, 0.415-0.752; specificity, 0.737; sensitivity, 0.481) for predicting cutaneous toxicity. RDI/BSA demonstrated limited discriminative ability for predicting cutaneous toxicity, suggesting this index alone may be insufficient as a robust clinical predictor. As the present exploratory analysis included a small, single-center cohort comprising exclusively Japanese patients, the generalizability of the estimated cut-off value is limited. Differences in body size, pharmacokinetics and treatment practices across ethnic groups may influence apalutamide exposure and toxicity. Therefore, the optimal RDI/BSA threshold may vary among populations. Notably, the cut-off value identified in the present study was lower than that previously reported (RDI/BSA ≥56) (19), which may reflect variations in patient characteristics, study design or sample size. Validation in larger, multiethnic cohorts is required to further determine exposure thresholds that minimize cutaneous toxicity while maintaining treatment efficacy.

The present single-center retrospective observational study has a number of limitations. First, despite existing predefined exclusion criteria, no patients were excluded on account of these, resulting in an unselected, real-world cohort. While this enhances the practical relevance of the present study, the lack of patient exclusions also raises the possibility that unmeasured comorbidities, pre-existing dermatologic conditions or concomitant medications may have contributed to toxicity or treatment outcome variabilities. Second, inherent biases associated with the retrospective design, including information and selection biases, could not be excluded and reliance on medical records introduces the possibility of incomplete data collection. Third, findings were based on a limited patient population and differences in baseline characteristics such as BSA and initial PSA levels between the groups may have influenced the observed outcomes. Although additional analyses adjusting for these variables were conducted using propensity score matching (data not shown), these analyses showed no notable differences in the incidence of cutaneous toxicity or progression-free survival between the standard- and reduced-dose groups. However, the limited sample size warrants cautious interpretation, as residual confounding cannot be completely excluded. Consequently, baseline differences, particularly those related to factors such as body size or tumor burden, may have influenced toxicity or treatment response independent of the dosing strategy. These limitations should be considered when interpreting the association between the dose-initiation approach and clinical outcomes. Fourth, the lack of significant differences in some endpoints (such as time to achieve PSA <0.2 ng/ml) may reflect insufficient statistical power rather than true equivalence. Furthermore, as this was a single-center study conducted exclusively in

Japanese patients, caution should be exercised when extrapolating the findings to other ethnic populations with different pharmacogenetic backgrounds or body compositions. In addition, published evidence on apalutamide-related cutaneous toxicity in non-Asian populations is limited, making it difficult to determine whether the exposure-toxicity patterns observed in East Asian cohorts apply to other racial or ethnic groups. The absence of comparable data from Western or African populations further constrains the global generalizability of the present findings. Future multicenter prospective studies, the development of individualized dosing strategies based on patient body size and the evaluation of long-term outcomes such as overall survival and PFS are warranted.

In conclusion, the findings of the present study suggest that initiating apalutamide at a reduced dose with stepwise escalation may decrease the risk of cutaneous toxicities in Japanese patients with a small BSA, while potentially mitigating adverse events, without compromising short-term efficacy. Furthermore, the present study highlights the importance of careful monitoring and dose adjustment during the first 2-3 months of treatment. Establishing individualized dosing protocols that incorporate body size and adverse event risk is an important step toward optimizing apalutamide therapy.

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Availability of data and materials

The data generated in the present study are not publicly available due to restrictions imposed by patient consent and institutional regulations but may be requested from the corresponding author.

Authors' contributions

TM and MK designed the study. TM, MG, SY, MN, HM and RM collected the data. TM analyzed and interpreted the data and wrote the manuscript. MG, SY, MN, HM and RM interpreted data. MK and EU interpreted data and revised the manuscript. All authors have read and approved the final manuscript. TM and MK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan and was approved by the Ethics Committee of Ogaki Municipal Hospital (approval no. 20251225-7h). The present study did not involve the collection of any new samples or information but was conducted solely using existing data, therefore written or verbal consent from the participants was not obtained. Instead, information regarding the present study was disclosed to the participants (through postings within the hospital or on the hospital website), thereby ensuring that the participants had the opportunity to opt out of the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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