

Risk Factors and Clinical Significance of Grade ≥ 3 Neutropenia During the First Cycle of Cabazitaxel Therapy With Primary Pegfilgrastim Prophylaxis in Metastatic Castration-resistant Prostate Cancer

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Abstract

Background/Aim: Cabazitaxel is an established treatment for metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-containing regimen; however, it is frequently associated with severe neutropenia. Although primary prophylaxis with pegfilgrastim is widely used, severe neutropenia still occurs. The present study aimed to identify risk factors for grade ≥ 3 neutropenia during the first cabazitaxel cycle (Cycle 1) under universal pegfilgrastim prophylaxis and to evaluate its clinical significance.

Patients and Methods: This retrospective study analyzed 40 patients with mCRPC treated with cabazitaxel at our institution between January 2015 and January 2025. All patients received primary prophylactic pegfilgrastim on day 3 of each cycle. The primary endpoint was the occurrence of grade ≥ 3 neutropenia during Cycle 1. A logistic regression analysis was performed to identify associated factors. Overall survival (OS) and progression-free survival (PFS) were analyzed using the Kaplan–Meier method and compared using the Log-rank test.

Results: Grade ≥ 3 neutropenia during Cycle 1 occurred in 18 patients (45.0%). A univariate analysis identified age ≥ 75 years and prior docetaxel exposure ≥ 9 cycles as significant risk factors for grade ≥ 3 neutropenia. In a multivariate analysis, prior docetaxel exposure ≥ 9 cycles was identified as an independent predictor. Febrile neutropenia occurred in six patients (15.0%) during Cycle 1. There were no significant differences in OS or PFS between patients with and without grade ≥ 3 neutropenia.

Conclusion: Despite universal pegfilgrastim prophylaxis, severe neutropenia during the first cabazitaxel cycle remains common, particularly in patients with extensive prior docetaxel exposure. However, early grade ≥ 3 neutropenia was

continued



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not associated with poorer survival outcomes. These results suggest that under adequate supportive care, early hematologic toxicity alone does not preclude continued cabazitaxel treatment.

Keywords: Metastatic castration-resistant prostate cancer, cabazitaxel, neutropenia, pegfilgrastim, primary prophylaxis.

Introduction

Cabazitaxel is an established treatment for patients with metastatic castration-resistant prostate cancer (mCRPC) who exhibit disease progression after docetaxel-based chemotherapy. The pivotal TROPIC trial demonstrated that cabazitaxel plus prednisone prolonged overall survival (OS) significantly more than mitoxantrone, thereby establishing cabazitaxel as a standard post-docetaxel therapy for mCRPC (1). Despite its proven efficacy, cabazitaxel is frequently associated with hematologic toxicity, particularly severe neutropenia, which remains a major concern in routine clinical practice.

To mitigate the risk of febrile neutropenia, primary prophylaxis with pegfilgrastim has been widely adopted during cabazitaxel treatment. Clinical studies in Japan showed that prophylactic pegfilgrastim reduced the incidence of febrile neutropenia in patients with mCRPC treated with cabazitaxel (2). Nevertheless, clinically significant grade ≥ 3 neutropenia still occurs in a high percentage of patients despite routine pegfilgrastim prophylaxis, indicating that preventive strategies alone may not completely eliminate early hematologic toxicity. It is also important to note that in many studies that evaluated cabazitaxel-associated neutropenia, the use of granulocyte colony-stimulating factor was not uniform and primary prophylaxis was not routinely administered to all patients, making direct comparisons of early hematologic toxicity across studies challenging.

Studies on non-Japanese populations reported that patients at a high risk of cabazitaxel-induced severe neutropenia may be identifiable early during treatment, underscoring the importance of appropriate risk stratification (3). In addition, cabazitaxel-related hematologic toxicities have been shown to predominantly

occur during the early phase of treatment rather than accumulating over subsequent cycles, highlighting the clinical relevance of adverse events occurring during the first cabazitaxel cycle (Cycle 1) (4).

Furthermore, clinical evidence indicates that cabazitaxel may be administered to elderly patients, including those aged ≥ 75 or even ≥ 80 years, in real-world clinical settings (5, 6). Consistent with these findings, a recent review summarized accumulating evidence supporting the feasibility of cabazitaxel in elderly populations (7). Given the increased vulnerability of older patients to hematologic toxicity, a careful evaluation of the risk of neutropenia in this population is important.

Despite these findings, data that focus specifically on risk factors for severe neutropenia occurring during Cycle 1 under uniform primary prophylaxis with pegfilgrastim remain limited. Therefore, the present study aimed to identify risk factors for grade ≥ 3 neutropenia during Cycle 1 in patients with mCRPC receiving universal pegfilgrastim prophylaxis and also to examine the potential clinical significance of early severe neutropenia.

Patients and Methods

The present study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee at our institution (No. 21-088). The need to obtain informed consent from patients was waived because of its retrospective design; however, an opportunity to opt out from this study was provided through the institutional website.

This retrospective study included 40 consecutive Japanese patients with mCRPC who were treated with cabazitaxel at our institution between January 2015 and January 2025. All patients were diagnosed with

adenocarcinoma of the prostate based on histopathological findings from transrectal ultrasound-guided biopsy and exhibited disease progression after treatment with a docetaxel-containing regimen.

Cabazitaxel (20–25 mg/m²) was administered intravenously on day 1 of each cycle in combination with oral prednisone (5 mg twice daily). Treatment cycles were repeated every 3–4 weeks at the discretion of the treating physician. Primary prophylactic pegfilgrastim was administered on day 3 of each cycle in all patients. Dose reductions or treatment delays were permitted at the discretion of the treating physician.

The clinicopathological data of each patient assessed in this study were obtained from electronic medical records. Prior to the initiation of cabazitaxel, laboratory data, including prostate-specific antigen (PSA), hemoglobin, albumin (Alb), alkaline phosphatase, lactate dehydrogenase, C-reactive protein, and the absolute neutrophil count, were measured with standard clinical testing methods, and all patients underwent computed tomography of the chest, abdomen, and/or pelvis as well as bone scintigraphy to evaluate the baseline disease extent of prostate cancer. After the initiation of cabazitaxel, measurements of PSA in addition to hematologic, renal, and hepatic function tests were performed every 3–4 weeks, while the intervals of radiological examinations were selected at the discretion of each physician. Disease progression after the introduction of cabazitaxel was assessed based on the Prostate Cancer Working Group 3 criteria (8).

The primary endpoint of this study was the occurrence of grade ≥3 neutropenia during Cycle 1. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (9).

All statistical analyses were conducted using EZR software (Saitama Medical Center, Jichi Medical University, ver. 1.68) and *p*-values <0.05 were considered to indicate significant differences. Risk factors for grade ≥3 neutropenia during Cycle 1 were evaluated using a logistic regression analysis. Regarding continuous variables, optimal cut-off values were selected using a receiver operating characteristic curve analysis. OS and

Table I. Patient characteristics and treatment-related factors.

Variables	n (%)
Age*, years	72.5 (54-82)
BMI*, kg/m ²	20.6 (16.1-32.4)
ECOG PS	
0	19 (47.5)
1	15 (37.5)
2	6 (15.0)
Metastatic sites	
Bone	34 (85.0)
Lymph node	27 (67.5)
Liver	8 (20.0)
Lung	7 (17.5)
PSA at cabazitaxel initiation*, ng/ml	22.1 (0.28-470)
Hb*, g/dl	11.1 (7.4-15.4)
Alb*, g/dl	3.6 (2.9-4.4)
ALP*, IU/l	239 (53-2856)
LDH*, IU/l	213 (134-1524)
CRP*, mg/dl	0.14 (0.01-8.92)
ANC*, cells/μl	5100 (1524-14168)
Prior docetaxel therapy	40 (100)
Number of prior docetaxel cycles*	10 (2-37)
History of grade ≥3 neutropenia during prior docetaxel therapy	31 (77.5)
History of FN during prior docetaxel therapy	3 (7.5)
Cabazitaxel starting dose	
25 mg/m ²	8 (20.0)
20-22.5 mg/m ²	32 (80.0)

*Data are presented as medians (ranges). BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: Prostate-specific antigen; Hb: hemoglobin; Alb: albumin; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ANC: absolute neutrophil count; FN: febrile neutropenia.

progression-free survival (PFS) were estimated using the Kaplan–Meier method and compared using the Log-rank test. OS was defined as the time from cabazitaxel initiation to death from any cause, and PFS as the time from cabazitaxel initiation to radiographic and/or clinical progression or death, whichever occurred first.

Results

Forty patients with mCRPC treated with cabazitaxel were included in the analysis. Baseline patient characteristics are summarized in Table I. Median OS for the entire cohort was 13.7 months [95% confidence interval (CI)=9.0-27.1 months] and median PFS was 6.1 months (95% CI=4.8-11.8 months).

Table II. Univariate and multivariate analyses of factors associated with grade ≥ 3 neutropenia during the first cycle of cabazitaxel.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>p</i> -Value	OR (95% CI)	<i>p</i> -Value
Age (≥ 75 vs. < 75 years)	4.19 (1.10-15.9)	0.035	3.18 (0.76-13.3)	0.11
BMI (≥ 22 vs. < 22 kg/m ²)	0.92 (0.26-3.28)	0.90		
ECOG PS (≥ 2 vs. < 2)	1.27 (0.22-7.20)	0.79		
Bone metastasis (Yes vs. No)	0.79 (0.14-4.49)	0.79		
Lymph node (Yes vs. No)	0.59 (0.16-2.24)	0.44		
Liver metastasis (Yes vs. No)	0.68 (0.14-3.34)	0.64		
Lung metastasis (Yes vs. No)	0.43 (0.07-2.51)	0.35		
PSA at cabazitaxel initiation (≥ 50.4 vs. < 50.4 ng/ml)	0.41 (0.10-1.67)	0.22		
Hb (≥ 10.2 vs. < 10.2 g/dl)	0.29 (0.06-1.30)	0.11		
Alb (≥ 3.5 vs. < 3.5 g/dl)	0.98 (0.24-3.93)	0.97		
ALP (≥ 315 vs. < 315 IU/l)	0.29 (0.06-1.30)	0.11		
LDH (≥ 164 vs. < 164 IU/l)	0.12 (0.01-1.18)	0.069		
CRP (≥ 1.96 vs. < 1.96 mg/dl)	0.17 (0.02-1.57)	0.12		
ANC (≥ 5810 vs. < 5810 cells/ μ l)	0.32 (0.08-1.21)	0.094		
Number of prior docetaxel cycles (≥ 9 vs. < 9)	8.00 (1.47-43.4)	0.016	6.44 (1.13-36.6)	0.036
History of grade ≥ 3 neutropenia during prior docetaxel therapy (Yes vs. No)	1.03 (0.23-4.58)	0.97		
History of FN during prior docetaxel therapy (Yes vs. No)	2.62 (0.22-31.6)	0.45		
Cabazitaxel starting dose (25 vs. 20-22.5 mg/m ²)	0.68 (0.14-3.34)	0.64		

OR: Odds ratio; CI: confidence interval; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PSA: prostate-specific antigen; Hb: hemoglobin; Alb: albumin; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; CRP: C-reactive protein; ANC: absolute neutrophil count; FN: febrile neutropenia.

Grade ≥ 3 neutropenia during Cycle 1 occurred in 18 of the 40 patients (45.0%). Univariate and multivariate logistic regression analyses were performed to identify factors associated with grade ≥ 3 neutropenia during Cycle 1, and the results obtained are shown in Table II. The univariate analysis identified age ≥ 75 years and prior docetaxel exposure ≥ 9 cycles as significant risk factors for grade ≥ 3 neutropenia. In the multivariate analysis, prior docetaxel exposure ≥ 9 cycles remained an independent factor associated with grade ≥ 3 neutropenia during Cycle 1, whereas age ≥ 75 years did not retain significance. Febrile neutropenia occurred in six of the 40 patients (15.0%) during Cycle 1.

Kaplan–Meier survival analyses revealed no significant difference in OS between patients who developed grade ≥ 3 neutropenia during Cycle 1 and those who did not (Figure 1). Median OS was 23.1 months (95%CI=10.0-42.3 months) in patients with grade ≥ 3 neutropenia and

10.2 months (95%CI=6.2-27.1 months) in those without grade ≥ 3 neutropenia (Log-rank $p=0.41$).

No significant difference was noted in PFS between the two groups (Figure 2). Median PFS was 8.7 months (95% CI=4.8-19.5 months) in patients with grade ≥ 3 neutropenia and 4.8 months (95% CI=2.5-14.5 months) in those without grade ≥ 3 neutropenia (Log-rank $p=0.97$).

Discussion

Cabazitaxel was established as a standard post-docetaxel therapy for mCRPC based on the survival benefit demonstrated in the pivotal TROPIC trial (1). Despite its proven efficacy, hematologic toxicity, particularly severe neutropenia, has remained a major concern in routine clinical practice and continues to complicate optimal treatment delivery (1, 2).

In Japan, primary prophylaxis with pegfilgrastim has been widely adopted to reduce the incidence of

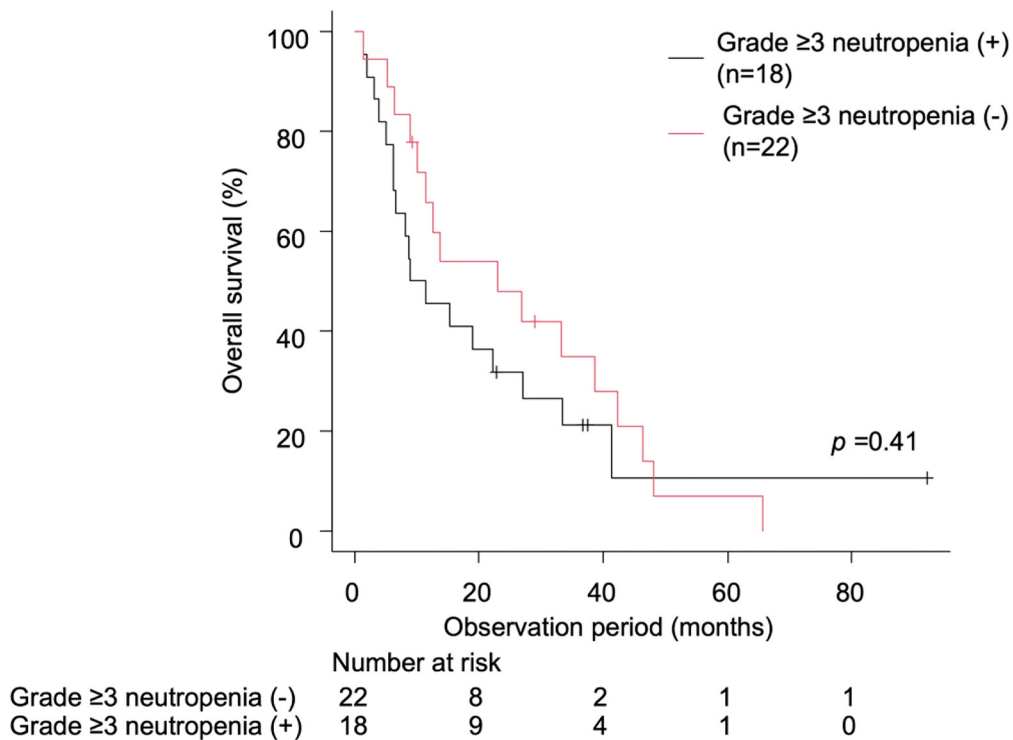


Figure 1. Overall survival (OS) according to the occurrence of grade ≥ 3 neutropenia during the first cycle (Cycle 1) of cabazitaxel treatment. Kaplan-Meier curves comparing overall survival between patients who developed grade ≥ 3 neutropenia during Cycle 1 and those who did not. Survival distributions were compared using the log-rank test.

febrile neutropenia during cabazitaxel therapy. Previous Japanese studies demonstrated that prophylactic pegfilgrastim effectively reduced febrile neutropenia (2). The present study exclusively evaluated patients who uniformly received primary prophylactic pegfilgrastim, thereby minimizing heterogeneity related to supportive care strategies. Nevertheless, grade ≥ 3 neutropenia during Cycle 1 occurred in nearly 50% of patients, indicating that pegfilgrastim does not completely prevent early hematologic toxicity and highlighting the need for further risk stratification even under standardized prophylaxis.

An important result of this study is that extensive prior exposure to docetaxel (≥ 9 cycles) was independently associated with the occurrence of grade ≥ 3 neutropenia during Cycle 1. This relationship is biologically plausible because prolonged exposure to taxane-based chemotherapy may impair bone marrow reserve and

reduce hematopoietic recovery, thereby predisposing patients to early severe neutropenia upon subsequent cytotoxic treatment. Importantly, cabazitaxel-related hematologic toxicities have been reported to occur predominantly during the early phase of treatment rather than accumulating over successive cycles, underscoring the clinical relevance of focusing on Cycle 1 events (4). In a Japanese real-world cohort, Yasuoka *et al.* reported that baseline PSA, hemoglobin level, and prior docetaxel exposure were independently associated with OS in Japanese patients treated with cabazitaxel (10). Interestingly, while prior docetaxel exposure was linked to survival outcomes in their cohort, our findings suggest that extensive prior exposure may also reflect cumulative treatment burden and impaired marrow reserve. Thus, prior docetaxel therapy may have dual clinical implications in the cabazitaxel setting.

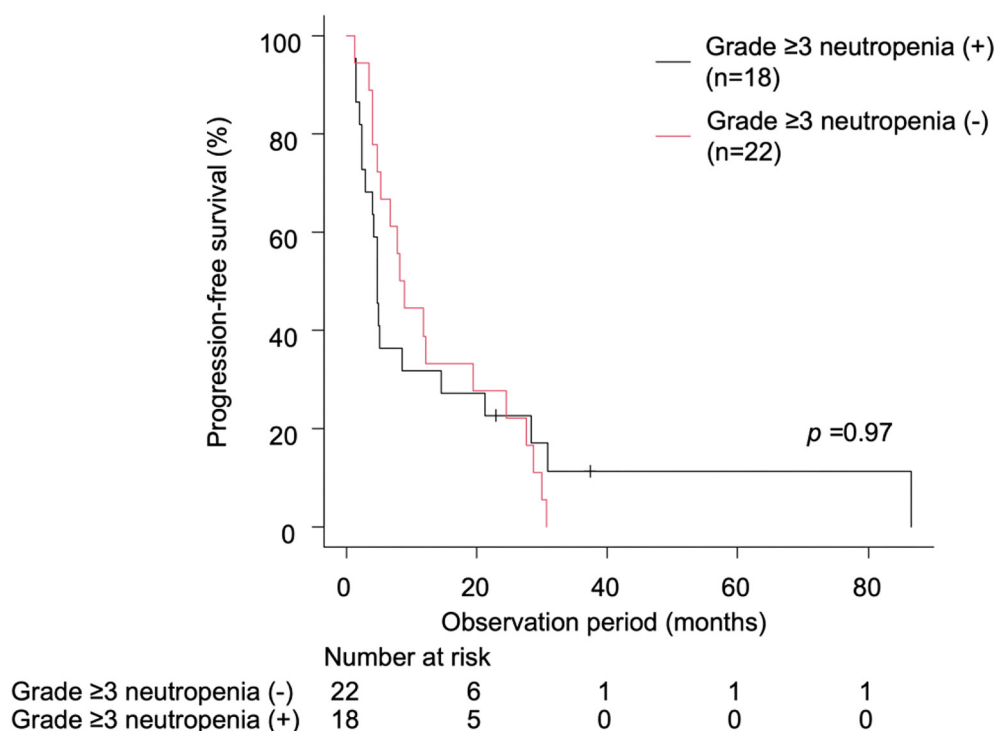


Figure 2. Progression-free survival (PFS) according to the occurrence of grade ≥ 3 neutropenia during the first cycle (Cycle 1) of cabazitaxel treatment. Kaplan–Meier curves comparing PFS between patients who developed grade ≥ 3 neutropenia during Cycle 1 and those who did not. Survival distributions were compared using the log-rank test.

The optimal starting dose of cabazitaxel remains an important issue in clinical practice. The PROSELICA trial demonstrated that a reduced dose of 20 mg/m² was not inferior to the standard 25 mg/m² dose with a more favorable safety profile (11). However, in real-world Japanese settings, starting dose often varies according to physician judgment and previous treatment history rather than protocol-defined criteria (2, 5, 6). In the present study, the cabazitaxel starting dose was not identified as a significant predictor of Cycle 1 severe neutropenia, suggesting the greater impact of treatment history than that of the initial dose. In the Prosty II trial, biweekly cabazitaxel (16 mg/m² on day 1 and day 14 of a 4-week cycle) was reported to be feasible, with a relatively low rate of grade ≥ 3 neutropenia, while maintaining antitumor activity (12). This observation indicates that treatment schedule modification may influence hematologic toxicity beyond supportive care alone.

Previous studies reported that cabazitaxel-induced severe neutropenia may be associated with improved survival outcomes, potentially reflecting higher effective drug exposure. Post hoc analyses of the TROPIC trial revealed the favorable prognostic impact of grade ≥ 3 neutropenia (13), and similar findings were observed in a Japanese cohort (14). Collectively, these findings support the hypothesis that severe neutropenia may serve as a surrogate marker of adequate systemic exposure to cabazitaxel. In line with this concept, practical predictors of severe neutropenia have been examined in real-world settings, including pharmacokinetic analyses demonstrating that higher early cabazitaxel exposure was associated with subsequent severe neutropenia (3). Furthermore, a recent Japanese study reported that the dose-to-albumin ratio predicted severe neutropenia, suggesting Alb as a pragmatic surrogate marker of

effective drug exposure in real-world practice (15). Urabe *et al.* further demonstrated that patients maintaining a relative dose intensity of >60% had significantly better PFS and OS (16), suggesting that preserving dose intensity may be clinically meaningful when toxicity is manageable.

However, the prognostic significance of cabazitaxel-induced neutropenia remains controversial. A recent systematic review and meta-analysis by Yanagisawa *et al.* demonstrated that the relationship between treatment-related neutropenia and survival outcomes was inconsistent and highly dependent on the clinical context, treatment sequence, and patient characteristics (17). Moreover, the large French FUJI cohort, reflecting routine clinical practice, reported that experiencing at least one grade ≥ 3 adverse event during cabazitaxel treatment, including hematologic toxicities, was independently associated with shorter OS, and was also associated with shorter PFS in a multivariate analysis (18). Importantly, prophylactic G-CSF use was not uniform in the FUJI cohort, highlighting real-world heterogeneity in supportive care. These findings suggest that severe toxicity sometimes captures underlying patient frailty or a limited physiological reserve rather than adequate drug exposure alone. Consistent with this perspective, Iwamoto *et al.* demonstrated that sarcopenia assessed by skeletal muscle index and the presence of visceral metastasis at cabazitaxel initiation were independently associated with poorer OS (19). These findings emphasize the importance of baseline frailty and disease burden when interpreting treatment-related hematologic toxicity.

Taken together, these findings indicate that grade ≥ 3 neutropenia cannot be uniformly interpreted as a favorable prognostic marker. Its clinical implications appear to be dependent on the context and affected by patient characteristics, treatment history, and the intensity and uniformity of supportive care. In our cohort, conducted under universal primary prophylaxis with pegfilgrastim, early grade ≥ 3 neutropenia during Cycle 1 was not associated with longer OS or PFS, supporting a cautious interpretation of treatment-related hematologic toxicity in real-world practice.

Elderly patients represent an increasingly important population in the management of mCRPC. Real-world studies have demonstrated that cabazitaxel may be administered to patients aged ≥ 75 and even ≥ 80 years with acceptable safety when appropriate supportive care is provided (5, 6). In our cohort, advanced age was associated with severe neutropenia in the univariate analysis, but did not retain significance in the multivariate analysis, showing that the cumulative treatment burden rather than chronological age alone may be more relevant for predicting early hematologic toxicity.

Limitations. The retrospective design limits generalizability, and the small sample size reduces statistical power. In addition, cabazitaxel dosing and treatment intervals were selected at physician discretion, which reflects real-world practice, but also introduces heterogeneity. Furthermore, the analysis focused exclusively on Cycle 1 and did not assess cumulative or late-onset toxicities. Therefore, these results need to be interpreted as hypothesis-generating and warrant validation in larger prospective studies.

Despite these limitations, the present study provides real-world evidence under uniform primary prophylaxis with pegfilgrastim and identifies extensive prior docetaxel exposure as a clinically relevant predictor of early severe neutropenia. A careful baseline assessment and intensified monitoring during Cycle 1, particularly in heavily pretreated patients, may facilitate safer and more individualized cabazitaxel administration in routine clinical practice.

Conclusion

In this real-world cohort uniformly receiving primary pegfilgrastim prophylaxis, grade ≥ 3 neutropenia during the first cabazitaxel cycle was common and was independently associated with extensive prior docetaxel exposure. However, early severe neutropenia was not associated with inferior survival outcomes. These results suggest that under adequate supportive care, early hematologic toxicity alone does not need to prompt the premature discontinuation of cabazitaxel, even in heavily pretreated patients.

Conflicts of Interest

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

Authors' Contributions

Research conception and design: Ryo Sato. Data acquisition: Ryo Sato, Yukihiro Yoshimi, Tetsuharu Nishio and Yu Matsunaga. Statistical analysis: Ryo Sato. Data analysis and interpretation: Ryo Sato. Drafting of the manuscript: Ryo Sato. Critical revision of the manuscript: Rikiya Matsumoto. Supervision: Rikiya Matsumoto.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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