RESEARCH ARTICLE

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Clinical Management of Potential Toxicity of Abemaciclib and Approaches to Ensure Treatment Continuation

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Abstract

Introduction: The association between abemaciclib dose reduction and treatment adherence is not clear. In this study, we examined real-world data of Japanese patients with advanced breast cancer (ABC) to determine how abemaciclib dose reduction is related to treatment continuation. **Methods:** This retrospective observational study involved 120 consecutive patients with ABC who received abemaciclib from December 2018 to March 2021. The time to treatment failure (TTF) was estimated using the Kaplan–Meier method. Univariate and multivariate analyses were performed to identify factors associated with a TTF of >365 days (TTF365). **Results:** According to the dose reduction during treatment, the patients were classified into 100, 200, and 300 mg/day abemaciclib groups. The 300 mg/day group had a TTF of 7.4 months, whereas the 100 and 200 mg/day groups had significantly longer TTFs (17.9 and 17.3 months, respectively; P = 0.0002). In this study, relative to the 300 mg/day arm, TTF was improved in 200mg/day arm and 100 mg/day arm (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.33–0.93) and [HR], 0.37; 95% CI, 0.19–0.74). For patients who received 300mg/day of abemaciclib dose arm, 200mg/day, and 100mg/day, the median TTF was 7.4 ,17.9 and 17.3 months. The frequently reported adverse effects (AEs) were anemia, increased blood creatinine levels, diarrhea, and neutropenia (90%, 83%, 83%, and 75% of the patients, respectively). Neutropenia, fatigue, and diarrhea were the top AEs causing dose reduction. A multivariate analysis that examined factors associated with achieving TTF 365 confirmed that dose down was an important factor (odds ratio: 3.95, 95% confidence interval: 1.68-9.36, P = 0.002). **Conclusions:** In this study, the 100 and 200 mg/day groups had a longer TTF than the 300 mg/day group, and dose reduction was identified as an important factor in achieving longer TTF.

Keywords: Metastatic breast cancer- abemaciclib- dose reduction- appropriate supportive care

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Introduction

Hormone receptor-positive/human epidermal growth factor 2-negative (HR+/HER2−) breast cancer accounts for almost two-third of breast cancer diagnoses (Castrellon, 2017; Lumachi et al., 2011). Abemaciclib is a cyclin-dependent kinase (CDK) 4/6 inhibitor, second only to palbociclib for the treatment of HR+/HER2− advanced breast cancer (ABC) (AlFakeeh and Brezden-Masley, 2018; Corona and Generali, 2018) . Current guidelines recommend abemaciclib as the first-line therapy in combination with a nonsteroidal aromatase inhibitor (NSAI) or fulvestrant in patients with HR+/HER2− ABC(Cardoso et al., 2020; Goetz et al., 2020; Goetz et al., 2017; Inoue et al., 2021; Sledge et al., 2020; Sledge et al., 2017; Takahashi et al., 2022) . The safety data from the MONARCH 2 and MONARCH 3 clinical trials have identified diarrhea, neutropenia, and anemia as the major adverse effects (AEs) associated with the use of abemaciclib (Goetz et al., 2017). Diarrhea was experienced by most patients who received abemaciclib in combination with fulvestrant (86%) or NSAI (81%). Neutropenia was also the most frequently reported serious (grade 3) AE in patients (27%) who received abemaciclib in combination with fulvestrant (Goetz et al., 2017; Sledge et al., 2017). The dose of abemaciclib was reduced in 142 (43.4%) patients owing to adverse events (Rugo et al., 2021). An interruption of abemaciclib therapy as a result of an adverse event occurred in 184 (56.3%) patients. A total of 64 (19.6%) patients in the abemaciclib arm discontinued the drug as a result of adverse events.

It is important to understand the risk factors for frequent AEs to avoid dose reduction and treatment interruption. The risk factor for grade 3 diarrhea, an important AE of

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abemaciclib, has been reported to be an age of 70 years or older, and risk factors for grade 3 neutropenia have been reported to be the performance status, Asian ethnicity, and white blood cell count before treatment (Modi et al., 2021). For successful continuation of abemaciclib therapy, it is considered necessary to understand these risk factors and maximally avoid dose reduction due to adverse events by appropriate management of abemaciclib AEs.

The management of adverse events during abemaciclib therapy requires the joint involvement of pharmacists (drug interactions and pharmacokinetics) and physicians who have different perspectives. In addition to consultations with physicians for outpatients, hospital pharmacists conduct interviews, and drugstore pharmacists conduct telephone follow-ups to provide necessary supportive care. Such pharmacist interventions in outpatients have been reported to prolong the time to treatment failure (TTF) (Todo et al., 2019) and maintain a high daily intake (Kimura et al., 2017) for therapeutic agents. The intervention and collaboration of an outpatient pharmacy are necessary for the management of AEs of abemaciclib, for which self-medication at home is considered important. The Breast Surgery and Pharmacy Departments at the Hokkaido Cancer Center provide necessary supportive care to outpatients via interviews conducted by hospital pharmacists and telephone follow-ups conducted by pharmacy pharmacists, in addition to physician consultations. However, there are no useful intervention reports related to the continuation of abemaciclib therapy. In this study, we aimed to investigate factors that contribute to the successful continuation of abemaciclib therapy.

Materials and Methods

Patient population and assessment

A total of 120 patients who received abemaciclib therapy at the Department of Breast Surgery, Hokkaido Cancer Center, between January 2018 and June 2021, were included in this study. This study was approved by the ethics committee of Hokkaido Cancer Center (Approval No. R3-25). This study adheres strictly to the 1975 Helsinki Declaration and the 1989 revised Hong Kong Declaration. All patients provided written informed consent to participate in the study. Histopathological data, the history of concomitant hormonal therapy and chemotherapy, the site of metastasis at the start of treatment, duration of treatment, adverse events and the time of their occurrence, the time of and reason for a dose reduction, and the time of and reason for treatment discontinuation were collected retrospectively from medical records.

Assessment of the timing of AEs and intervention

The evaluation of AEs covered a 4-week period to record AEs and determine the need for dose reduction and whether to continue treatment. Pharmacists were also interviewed to assess AEs and consulted with physicians to determine dosage adjustment. Depending on the results of the discussion, a guidance on supportive care, which was tailored to individual outpatients, was provided by the pharmacist.

Predictors and outcome evaluation

The incidence of AEs, reasons for treatment discontinuation and dose reduction, and TTF were investigated in this study. The primary goal was to identify factors that help to achieve time to abemaciclib treatment failure of more than 365 days (TTF365). The TTF was measured from the date of abemaciclib initiation to that of abemaciclib termination. Assessment variables were selected based on the availability, similar or prior evidence, and medical validity. The assessed pretreatment variables were age, prior chemotherapy, line of treatment, combination hormone therapy, liver, and bone metastases, body mass index, and neutrophil-to-lymphocyte ratio. The assessed post-treatment variables were dose reduction of abemaciclib and number of AEs (within 1 year of the onset).

To confirm the effectiveness of supportive care, AEs were classified as avoidable if they could be prevented entirely or prevented from becoming serious with the aid of supportive care and as unavoidable if they could not. Nonhematologic toxicities such as diarrhea, nausea, and skin rash were defined as avoidable AEs. On the contrary, hematologic toxicities such as neutropenia and anemia were defined as unavoidable AEs. The time to dose reduction due to the defined AEs in each group was calculated based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

Pharmaceutical interventions

The hospital pharmacist interviewed the patients in a separate room between their arrival at the hospital and examination after blood collection. All data obtained by the pharmacist, including symptoms, medication adherence, and the presence of AEs, were entered into electronic medical records to facilitate information sharing among different medical professionals. In addition, pharmacists provided ongoing supportive care and medication guidance to patients and checked their awareness and knowledge of AEs, symptom management, and medication adherence. For patients who complained of moderate to severe AEs, pharmacists suggested treatments to physicians to reduce AEs. After meeting the patient, the hospital pharmacist contacted dispensing pharmacies with information on new prescriptions and supportive care. The pharmacy pharmacists reviewed this information and conducted a telephone follow-up. A telephone follow-up program was created, and dispensing pharmacies performed telephone follow-ups when AEs of abemaciclib were likely to occur. In this telephone follow-up, we confirmed the occurrence of AEs requiring immediate medical attention and confirmed the use of supportive care drugs. This system allowed us to monitor abemaciclib AEs and adherence. If the results of a telephone follow-up with a patient indicated an AE requiring immediate action or medical staff intervention was required, we asked the hospital pharmacist to submit a report. This report was shared with doctors, and the patient was provided consultation and advice as needed. This helped prevent AEs from becoming more serious by

responding before the next visit.

Statistical analysis

Statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan) and EZR package of R. The t-test, Mann–Whitney U-test, and Fisher's exact test were used for statistical analysis. The relationship between the dose reduction of abemaciclib and TTF was analyzed using Cox proportional hazards model. Depending on the final dose, the TTF300, TTF200, and TTF100 were calculated for the 300, 200, and 100 mg/day groups, respectively. Univariate and multivariate analyses was performed to identify the factors that could help achieve the TTF365. Results with $P < 0.05$ were considered statistically significant.

Results

Patient population and background

The characteristics of the participants are shown in Table 1. The median age of the patients at the start of treatment was 57 (interquartile range: 50–70) years. A total of 51% of the patients had received prior chemotherapy. Hormone therapy for advanced recurrent breast cancer was 48% for the first-line treatment, 23% for the second-line treatment, and 29% for the third- or higher-line treatment. The metastatic sites at the start of treatment were the liver in 37% and bone in 64% of the patients. The hormonal agents used in combination with abemaciclib were aromatase inhibitors in 28% and fulvestrant in 72% of the patients.

Table 1. Characteristics of Patients

Characteristic	
Age (years) Mean (IQR)	57 (50-70)
BMI Mean (IQR)	22 (20-25)
Site of metastasis (Number)	
Lung	29
Lymph nodes	38
Liver	45
Bone	78
Other	10
Therapy line (1 / 2/ >3)	57/28/35
Laboratory test values (Median)IQR))	
AST	26 (21-36)
ALT	20 (14-36)
Serum creatinine	0.65 (0.56-0.74)
White blood cells	5200 (4200-6600)
Hemoglobin	12.7 (11.8-13.4)
Platelet	22.6 (19.4-26.5)
Neutrophils	2900 (2200-3900)
Albumin	4.1 (3.8-4.2)
NLR (neutrophil to lymphocyte ratio)	1.9 (1.4-3.0)
PLR (platelet to lymphocyte ratio)	150 (100-210)
LMR (lymphocyte to monocyte ratio)	5.3 (4.1-6.7)
Dose reduction (Number (%))	
1-level dose down	84 (70%)
2-level dose down	24 (20%)

IQR, interquartile range.

Final dose levels and TTFs

According to the dose reduction during treatment, the patients were classified into 100, 200, and 300 mg/day abemaciclib groups. The 300 mg/day group had a median TTF of 7.4 months, whereas the 100 and 200 mg/day groups had significantly longer median TTFs (17.9 and 17.3 months, respectively; $P = 0.0002$). In this

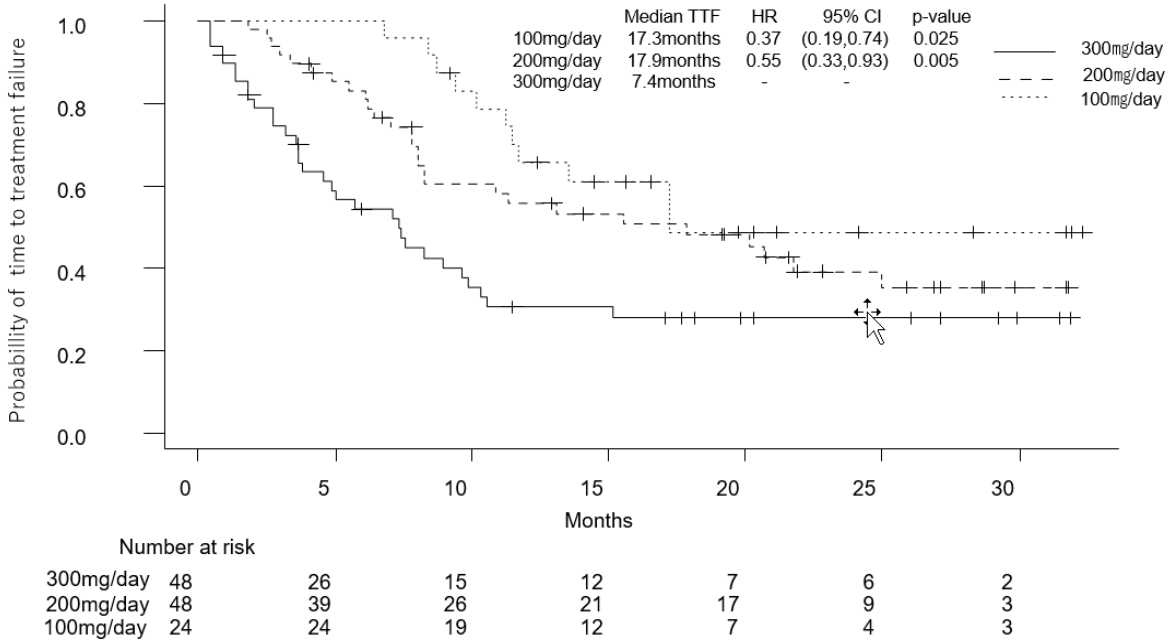

Figure 1. Each Final Dose Level and Time to Treatment Failure (n=121). Time to treatment failure of the patient population enrolled in this study by treatment line. Solid line, Daily dose 300 mg ; dashed line, Daily dose 200 mg;dotted line Daily dose 100 mg.

Table 2. Adverse Events that Occurred in >10 Patients

Preferred term	All grade	Grade 3-4	Grade 2-4
Anemia	90%	8%	47%
Blood creatinine increased	83%	0%	14%
Diarrhea	82%	6%	36%
Neutropenia	75%	33%	70%
Leukopenia	75%	13%	63%
Alanine aminotransferase increased	74%	14%	25%
Aspartate aminotransferase increased	72%	7%	18%
Thrombocytopenia	64%	4%	8%
Fatigue	43%	2%	18%
Nausea	39%	4%	14%
Rash	31%	1%	23%
Stomatitis	23%	1%	11%
Decreased appetite	23%	3%	13%
Nail loss (concurrent nail ridging)	18%	0%	0%
Dysgeusia	16%	0%	5%
Eye disorders	9%	0%	1%
Alopecia	7%	0%	0%
Pruritus	6%	0%	0%
Eczema	5%	0%	0%
Vomiting	5%	0%	2%
Gastrointestinal disorders	4%	0%	1%
Interstitial pneumonia	3%	1%	3%
Stomach pain	3%	0%	1%
Cough (dyspnea)	3%	0%	2%
Dry skin	3%	0%	0%
Dizziness	2%	0%	0%
Arthralgia	2%	0%	0%
Hypertension	2%	1%	2%
Edema peripheral	2%	0%	1%
Watering eyes	2%	0%	0%

Table 3. Reasons for One- and Two-Level Dose Reductions

N (%)	1-level dose reduction	2-level dose reduction
Neutropenia	24 (29%)	8 (33%)
Fatigue	14 (17%)	5 (21%)
Diarrhea	12 (14%)	4 (17%)
Anemia	7 (8%)	1 (4%)
Alanine /Aspartate aminotransferase increased	6 (7%)	3 (12%)
Decreased appetite	6 (7%)	1 (4%)
Nausea	5 (6%)	0 (0%)
Rash	3 (4%)	1 (4%)
Thrombocytopenia	2 (2%)	1 (4%)
Dysgeusia	2 (2%)	0 (0%)
Blood creatinine increased	1 (1%)	0 (0%)
Cough (dyspnea)	1 (1%)	0 (0%)
Pneumonitis	1 (1%)	0 (0%)
Total	84	24

study, relative to the 300 mg/day arm, median TTF was improved in 200 mg/day arm and 100mg/day arm (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.33–0.93) and [HR], 0.37; 95% CI, 0.19–0.74). For patients who received 300 mg/day of abemaciclib dose arm, 200 mg/day, and 100 mg/day, the median TTF was 7.4 ,17.9 and 17.3 months (Figure 1).

Frequencies of AEs

A cumulative total of 1,058 AEs were identified, which are summarized in Table 2. There were 372 (35%) AEs within the first month of treatment, and 59% of all AEs were observed in the first 3 months. The top five most frequent AEs were anemia, increased blood creatinine levels, diarrhea, neutropenia, and leukopenia. Anemia occurred in 91% of patients, 9% of whom had grade 3 anemia.

Reasons for treatment discontinuation

The most common reason for treatment discontinuation

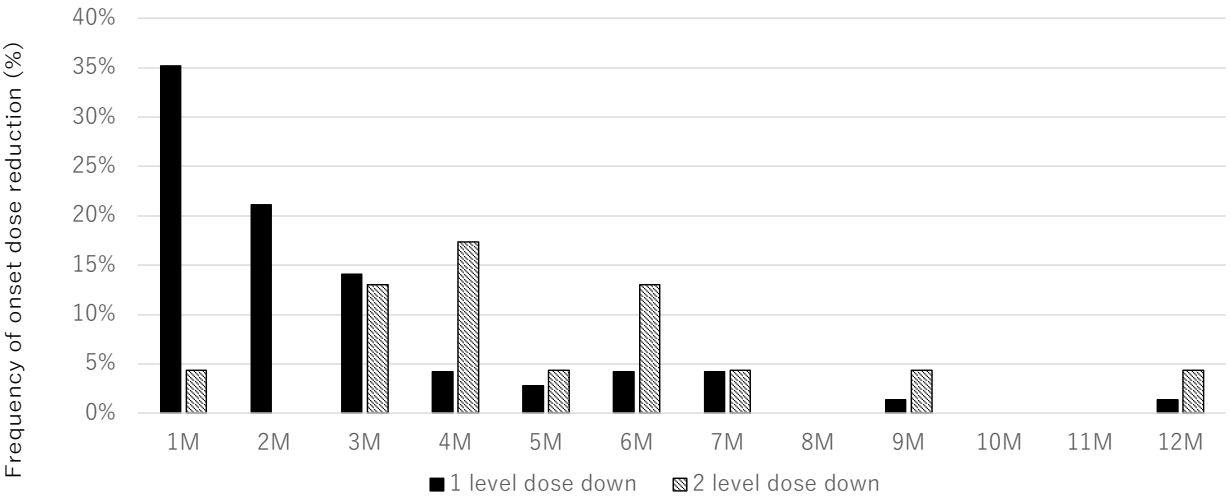

Figure 2. Transition in the Timing of Abemaciclib Dose Reduction. Filled bars presents 1-level dose reduction and shaded bars presents 2-level dose reductions.

Table 4. Univariate and Multivariate Analyses of Factors Associated with Achieving a Time to Abemaciclib Treatment Failure of >365 Days

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Treatment line				
(1st v.s. other)	2.56 (1.22-5.39)	0.01*	2.56 (1.22-5.39)	0.29
Count of adverse effects(within 1 year onset)				
(adverse effects >3 v.s. ≤3)	0.55 (0.22-1.40)	0.2	0.46 (0.15-1.37)	0.16
Age				
(>72v.s. ≤72)	0.54 (0.20-1.75)	0.22	0.70 (0.22-2.28)	0.56
BMI				
(>22v.s. ≤22)	0.96 (0.49-2.01)	0.91	Excluded	
Albumin				
(>4.2 v.s. ≤4.2)	2.11 (0.91-4.56)	0.05	1.22 (0.53-2.81)	0.64
NLR				
(>3.0 v.s. ≤3.0)	0.66 (0.25-1.75)	0.4	Excluded	
Dose reduction				
(dose reduction v.s. full dose)	3.55 (1.60-7.90)	0.002**	3.95 (1.68-9.36)	0.002**

*, p< 0.05; **, p< 0.01; CI, confidence interval.

was progressive disease in 35 patients, followed by interstitial pneumonia in 10, patient convenience (financial problems) in 6, liver dysfunction in 4, anorexia in 3, malaise in 2, neutropenia in 2, skin rash in 2, and other reasons in 9 patients. The discontinuation rate due to progressive disease was 100% in the group receiving the full dose, but this dropped to 54% overall in the two groups receiving reduced doses.

Reasons for dose reduction

In total, 84 patients had a one-level dose reduction, including 24 (29%) due to neutropenia, 14 (17%) due to fatigue, and 12 (14%) due to diarrhea. Twenty-four patients had a two-level dose reduction, including 8 (33%) due to neutropenia, 5 (21%) due to fatigue, and 5 (21%) due to diarrhea (Table 3). The incidence of one-level dose reductions was the highest in the first month of treatment (35% of patients) and then gradually decreased. In contrast, two-level dose reductions peaked at 4 months post-dose and then decreased (Figure 2).

Factors associated with achieving the time to abemaciclib treatment failure of >365 days

The results of the univariate and multivariate analyses are shown in Table 4. The multivariate analysis revealed that dose reduction was the only effective factor that can be modified to achieve the TTF365 (odds ratio: 3.95, 95% confidence interval: 1.68–9.36, P = 0.002).

Cumulative frequency of dose reduction occurrences during abemaciclib treatment

A comparison of the times to dose reductions for avoidable and unavoidable AEs showed that the median value of the avoidable AE group was not reached and that

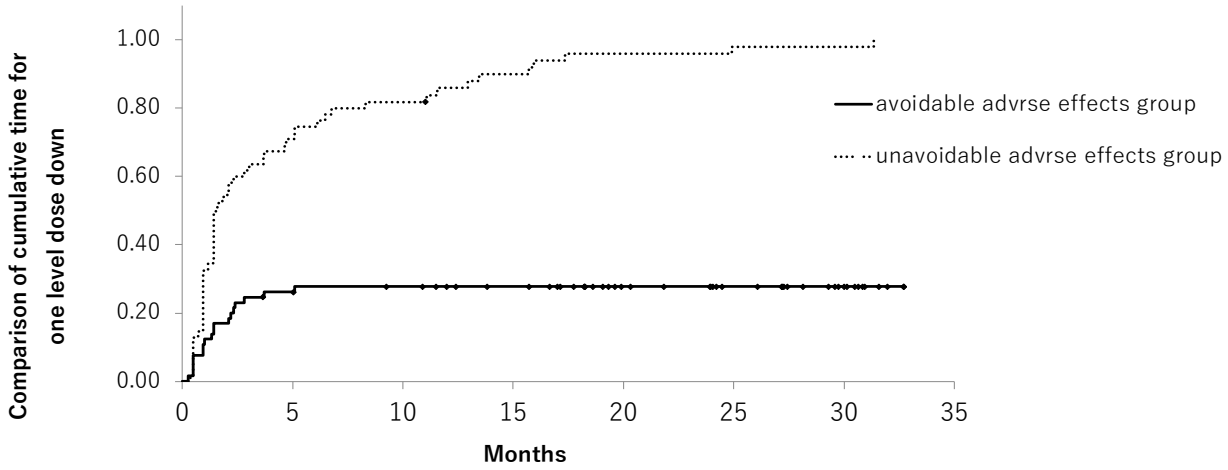

Figure 3. Cumulative Frequency of Dose Reduction Occurrences during Abemaciclib Treatment. Patients were divided into two groups: adverse events that could be avoided by prophylactic supportive care(solid lines) and those that could not be avoided(dashed lines), and the time to 1-level dose down was compared.

of the unavoidable AE group was 1.5 months (Figure 3). Importantly, the timing of dose reduction was earlier in the unavoidable AE group than in the avoidable group.

Discussion

To our knowledge, this is the first study to confirm that an appropriate dose reduction of abemaciclib is necessary for Japanese patients with ABC to successfully achieve a 1-year treatment period. This result suggests that dose reduction may be necessary even with adequate supportive care, depending on the AE. As an example, loperamide should be used aggressively for diarrhea, and dose reduction should be avoided whenever possible. On the contrary, dose reduction is unavoidable in the case of neutropenia. We believe that effective treatment can be achieved. The key to success is the active cointervention of physicians and hospital and drugstore pharmacists in the management of AEs in patients on abemaciclib therapy. The median time to dose reduction in the group of AEs (diarrhea, nausea, skin rash, and fatigue) that could be avoided with supportive care by cointervention was not attained. In contrast, in the group of serious AEs that could not be avoided (myelosuppression, hepatic dysfunction, and renal dysfunction), the median time to dose reduction was 1.5 months, which was significantly shorter. Therefore, it is necessary to divide the reasons for dose reductions into two groups, and it is important to manage AEs that can be avoided with supportive care cointervention. The point of this cointervention is that the drugstore pharmacist provides telephone support to the patient for the appropriate use of supportive care and early detection of AEs, and the hospital pharmacist reviews this information and provides feedback to the physician. Medication adherence is important in chemotherapy with oral anticancer agents. Direct intervention effects on medication adherence of patients receiving chemotherapy with oral anticancer agents and education by pharmacists on correct drug use and avoidance of AEs have been reported (Kimura et al., 2017; Todo et al., 2019). In this study, the total acceptance rate of prescription suggestions was over 95%. The reason for this high percentage is that pharmacists offer supportive care to outpatients and evaluate various perspectives when assessing treatment efficacy and adverse effects. In addition, pharmacists interview patients about their lifestyle, medication intake, and AE severity to comprehensively understand their needs. We believe that it is important for pharmacists with different perspectives to intervene.

In particular, the results of this study were comparable to those of a large clinical trial on diarrhea, which frequently occurs and reduces the quality of life. When the frequency of diarrhea was compared, it was 86.4% for all grades in the MONARCH 2 population and approximately 90.4% in the Asian population (Toi et al., 2021). Furthermore, the incidence of grade 3/4 diarrhea was reported to be 14.4% in the Asian population sub analysis compared with 13.4% in the entire population. Referring to the frequency of adverse drug reactions in Asians based on a sub analysis of the phase III clinical trial population, a high incidence of several adverse drug reactions, including diarrhea, nausea, and anorexia, has been reported, and thus, caution should be exercised in Japanese patients. However, in this study, the frequency of diarrhea was approximately 82% for all grades but as low as 6% for grade 3/4. In our study, one patient discontinued treatment because of nausea and two because of anorexia, but no patient discontinued treatment because of diarrhea. Pooled analysis of the MONARCH 2 and MONARCH 3 trials reported that 6 to 13 patients (1.8–2.9%) discontinued treatment because of diarrhea (Rugo et al., 2021). Therefore, comparison between the MONARCH 2 study and our results showed that the frequency of dose reduction due to diarrhea was the same, but serious events, such as treatment interruption, could be avoided. We believe that this is an important result that contributes to the prevention of serious events by creating a flowchart to support pharmacists in prescribing diarrhea medication and providing telephone support.

The timing and reasons for one- and two-level dose reductions of abemaciclib were also analyzed in this study. The results showed that the peak of the one-level dose reduction was in the first month of treatment at approximately 35%, followed by a gradual decrease by the sixth month; the two-level dose reduction peaked in the fourth month of treatment. Furthermore, the reasons for one-level dose reductions were neutropenia (33%), diarrhea (24%), and fatigue (21%), and those for two-levels dose reductions were similar: neutropenia (41%), diarrhea (24%), and fatigue (18%). These findings are consistent with those of the MONARCH 3 study, in which diarrhea, neutropenia, and fatigue were the top AEs of abemaciclib (Goetz et al., 2017) and the reasons for dose reduction.

In this study, it was also confirmed that the duration of successful treatment in the 200 and 100 mg/day groups were significantly prolonged, to 17.9 and 17.3 months, respectively, compared with 7.4 months in the 300 mg/day group; in the two groups, treatment was continued without a final dose reduction. The reason for the significantly prolonged successful treatment in the 100 and 200 mg/day dose groups could be that the blood concentration of abemaciclib is related to the occurrence of AEs. Therefore, we believe that the therapeutic effect was proportional because of sufficient exposure to the drug to force a reduction in the dose. It is believed that the active management of AEs from such sufficient exposure by the pharmacist did not lead to an avoidable early dose reduction or discontinuation but resulted in continued treatment, which significantly prolonged the successful treatment duration in the reduced dose group. Analyses of the overall MONARCH 2 and MONARCH 3 populations showed that the progression-free survival benefit of abemaciclib was not reduced by dose reduction (Rugo et al., 2021; Johnston et al., 2019), which supports dose reduction as a viable treatment option.

In addition, estrogen receptor 1(ESR1) mutations have been reported to be involved as one of the endocrine resistance factors (Yanagawa et al., 2017; Angus et al., 2017). The ESR1 mutations are more frequent in recurrent metastases than in primary tumors, ranging from 11.4% to 54.5% (Jeselsohn et al., 2014; Razavi et al., 2018), and

have been reported more frequently in liver metastases. In the present study, the incidence of liver metastases was 46% in the 300 mg/day group and 32% overall in the 100 and 200 mg/day groups, suggesting that the presence of ESR1 mutations may be related to a poor TTF.

This study has several limitations. First, it was a single-site study. Second, the number of patients was small (120 patients). Third, the median overall survival rate was not reached because of the short follow-up period of approximately 3 years. Thus, a longer follow-up period may provide new information.

In conclusions, in this our real-world, the 100 and 200 mg/day groups had longer TTFs than the 300 mg/day group when dose reduction was necessary despite adequate supportive care. Our study also showed the frequencies of adverse events that reduce the patients' quality of life, such as diarrhea and anorexia, were high, it is necessary for medical staff, including physicians and pharmacists, to practice appropriate supportive care, rather than easily reduce the abemaciclib dose because of preventable adverse effects. To clarify the relationship of a treatment outcomes and dose reduction of abemaciclib, further prospective research is necessary.

Author Contribution Statement

ST, HM, HH, SK, MK, NT, MT, and KW confirmed the medical assessment and designed this study. HM, NT, KW, and MT provided advice regarding statistical analyses. ST and HH performed the statistical analyses. ST and HH edited the manuscript. All authors have discussed the results and commented on the manuscript.

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Data availability

The data supporting the findings of this study are available from the corresponding author (TS) upon reasonable request.

Declaration of conflicting Interest

The authors declare no conflicts of interest.

Ethical approval and consent to participate

This study was approved by the ethics committee of Hokkaido Cancer Center (Approval No. R3-25). All patients provided written informed consent to participate in the study.

Consent for publication

Not applicable.

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