

Management of Severe Abemaciclib-induced Liver Dysfunction: Feasibility of Switching to Palbociclib

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Abstract

Background/Aim: Abemaciclib, a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, can cause severe liver injury, leading to treatment discontinuation. We report five cases of patients treated with a combined regimen of a CDK4/6 inhibitor and hormone therapy for metastatic breast cancer. Following the development of serious liver dysfunction (grade ≥ 3) during abemaciclib therapy, switching to palbociclib allowed continuation of CDK4/6 inhibitor treatment.

Case Report: The causative role of abemaciclib was assessed using the drug-induced liver injury scoring system (RECAM-J 2023), which evaluates multiple factors, including time to onset, course after onset, prior reports of liver injury, exclusion of other potential causes, and effects of re-administration. A score of ≥ 8 indicates a high likelihood of drug-induced liver injury; all five cases in this study met this criterion, with one case reaching a maximum score of 17. Because CDK4/6 inhibitors are administered alongside hormonal agents, we also evaluated the potential contribution of concomitant endocrine therapy. The likelihood of hormonal agents causing liver injury was assessed as "Possible." Each patient underwent further hepatological evaluation, including testing for viral hepatitis and autoimmune hepatitis. Based on these assessments, the hepatologist confirmed drug-induced liver injury. Following normalization of liver function test values, patients were switched to palbociclib. No recurrence of liver dysfunction was observed, allowing CDK4/6 inhibitor therapy to continue successfully.

Conclusion: These cases suggest that severe liver damage induced by abemaciclib, does not necessarily preclude continued CDK4/6 inhibitor therapy. Switching to palbociclib may be a feasible strategy, provided liver function has recovered before reinitiating treatment.

Keywords: Breast cancer, hepatotoxicity, drug-induced liver dysfunction, abemaciclib, palbociclib, CDK4/6 inhibitors.

Introduction

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, in combination with endocrine therapy, are the gold

standard for systemic treatment of patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC) (1-3).



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In early breast cancer (EBC) with HR+/HER2- status and lymph node involvement, the risk of recurrence is high (up to 30% within five years) necessitating intensive treatment (4). Two years of adjuvant abemaciclib combined with endocrine therapy (ET) has been designated as a Category 1 recommendation by the National Comprehensive Cancer Network (NCCN) and is recognized as the international standard of care. Despite its efficacy, abemaciclib is associated with significant adverse effects including hepatotoxicity. Pooled data from the MONARCH 2 and MONARCH 3 trials indicate that alanine aminotransferase (ALT) elevations occur in 15.1% of patients (all grades), with Grade 3 and 4 elevations in 4.8% and 0.3%, respectively (5). Aspartate aminotransferase (AST) elevations were reported in 14.2% (all grades) and 2.9% (Grade 3) of patients. Hepatic adverse events led to dose reductions in 1.6%–2.4% of cases and treatment interruptions in 0.5%–0.6%. Severe hepatic dysfunction can limit continued CDK4/6 inhibitor therapy, even in patients deriving clinical benefit. In Japan, where only abemaciclib and palbociclib are available, switching between these agents may provide an alternative strategy for maintaining CDK4/6 inhibitor therapy. However, data on rechallenging with CDK4/6 inhibitors following severe liver toxicity remain limited. This report provides real-world insights into the feasibility of reintroducing CDK4/6 inhibitors after discontinuation due to liver dysfunction. The case report was prepared in accordance with the CARE guidelines (6).

Case Report

This study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. Ethical approval in line with local and national guidelines was not required because the patient data were reviewed retrospectively. Sufficient precautions were taken to ensure that individuals could not be identified. Approval was obtained from the Ethics Review Committee of Hokkaido Cancer Center (Approval No. R3-25).

Case 1. A 72-year-old woman with MBC was started on a combination therapy with letrozole (1 mg/day) and abemaciclib (300 mg/day). On day 29, her ALT peaked at 586 IU/l. After discontinuation of abemaciclib, ALT levels decreased by half within approximately 1 month. Letrozole was continued, and abemaciclib was not reintroduced. Following the switch to palbociclib, ALT levels remained stable.

Case 2. A 71-year-old woman with MBC was initiated on letrozole (1 mg/day) and abemaciclib (300 mg/day). On day 27, her ALT peaked at 380 IU/l. Abemaciclib was discontinued, leading to a 50% reduction in ALT within 1 month. Her endocrine therapy was switched from letrozole to fulvestrant. Abemaciclib was not reintroduced, and ALT levels remained stable after transitioning to palbociclib.

Case 3. A 66-year-old woman with MBC was treated with fulvestrant (1,000 mg/day) and abemaciclib (300 mg/day). On day 43, her ALT peaked at 241 IU/l. After discontinuation of abemaciclib, ALT levels halved over 2 months. Endocrine therapy was changed from fulvestrant to anastrozole. Abemaciclib was not reintroduced, and ALT levels remained stable after initiating palbociclib.

Case 4. A 52-year-old woman with MBC received tamoxifen (20 mg/day) and abemaciclib (300 mg/day). On day 57, her ALT peaked at 1,361 IU/l. Abemaciclib was discontinued, resulting in a 50% reduction in ALT within 1 month. Upon reintroduction of abemaciclib, ALT rose again from 27 IU/l to 434 IU/l, prompting permanent discontinuation. She continued tamoxifen monotherapy for approximately 1 year. When palbociclib was later introduced, ALT levels remained stable.

Case 5. A 72-year-old woman with MBC was treated with fulvestrant (1,000 mg/day) and abemaciclib (300 mg/day). On day 58, her ALT peaked at 369 IU/l. After discontinuation of abemaciclib, ALT levels halved over 2 months. Abemaciclib was not reintroduced, and ALT levels remained stable after switching to palbociclib.

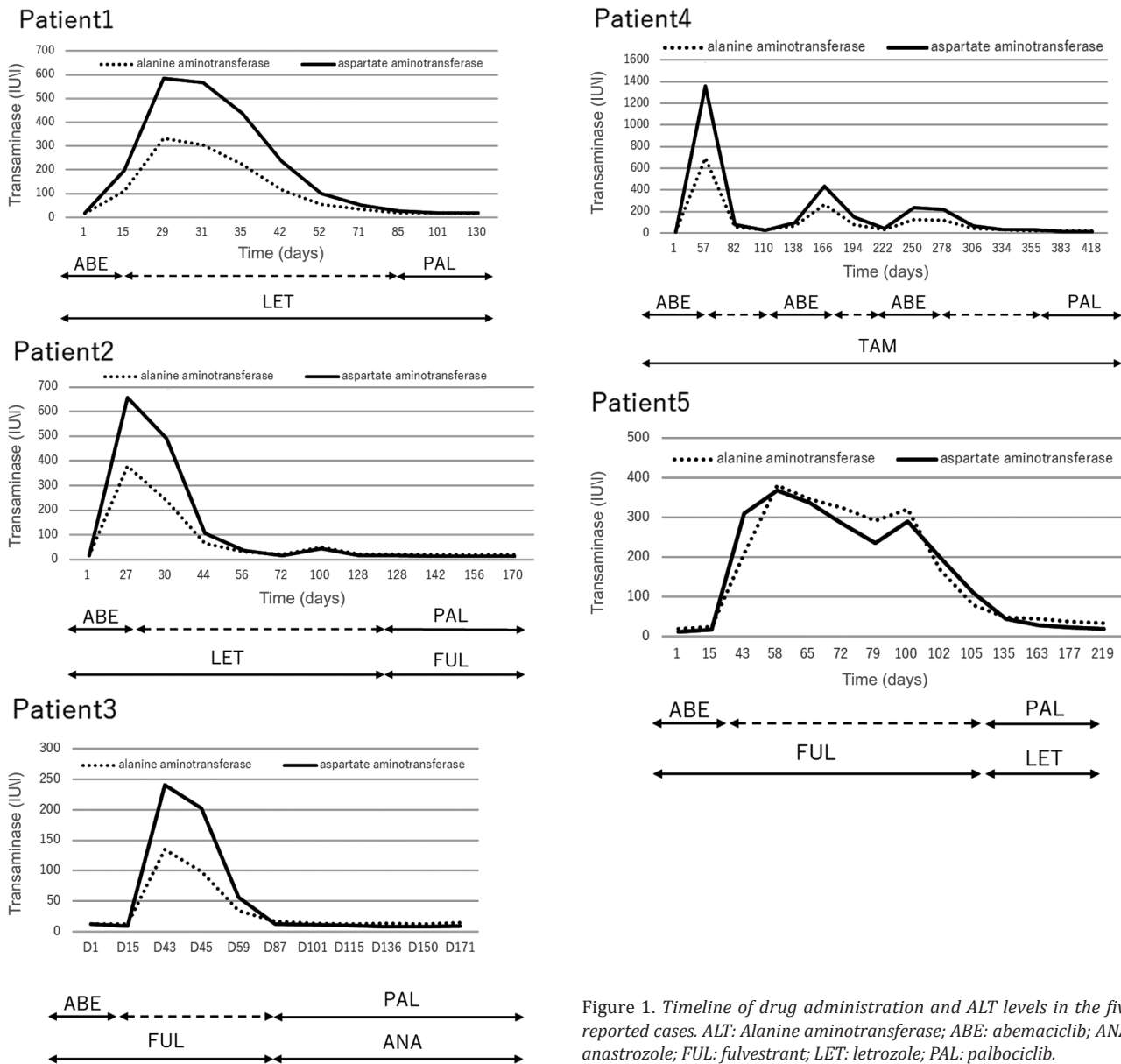


Figure 1. Timeline of drug administration and ALT levels in the five reported cases. ALT: Alanine aminotransferase; ABE: abemaciclib; ANA: anastrozole; FUL: fulvestrant; LET: letrozole; PAL: palbociclib.

Discussion

This case report is the first to document multiple patients who successfully transitioned to palbociclib, a CDK4/6 inhibitor, following severe liver dysfunction caused by abemaciclib, thereby allowing continued treatment without recurrence of hepatotoxicity. Previous reports indicate that

most cases of abemaciclib-induced liver dysfunction occur within 3 months of treatment initiation (7, 8). In our series, liver dysfunction developed within 2 months, consistent with and reinforcing the reproducibility of prior observations (Figure 1).

The precise mechanism underlying CDK4/6 inhibitor-induced liver dysfunction remains unclear. The predominant

Table I. *RECAM-J 2023 scoring of suspected drug-induced liver injury in five patients.*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Suspected drugs	ABE/LET	ABE/FUL	ABE/ANA	ABE/TAM	ABE/FUL
Time to onset (days)	4/4	4/4	4/4	4/4	4/4
Days from discontinuation to onset	0/0	0/0	0/0	0/0	0/0
Course after onset of liver damage	4/-6	4/-6	3/-6	4/-6	3/-6
Reports of previous liver damage	3/3	3/3	3/3	3/3	3/3
Exclusion of other causes (viral hepatitis, <i>etc.</i>)	0/0	0/0	0/0	0/0	0/0
Other factors (medical history, re-administration, biopsy, <i>etc.</i>)	0/0	0/0	0/0	6/0	0/0
Total score	11/1	11/1	10/1	17/1	10/1

pattern of injury is hepatocellular, and approximately 32% of affected patients exhibit autoimmune features such as positive antinuclear antibodies and/or elevated serum IgG levels at diagnosis (9). Some evidence suggests that corticosteroid therapy may aid recovery in cases where liver dysfunction does not resolve after discontinuation of CDK4/6 inhibitors; however, this approach has not been sufficiently validated and requires further study. Structural differences among CDK4/6 inhibitors appear to influence their hepatotoxicity profiles. While ribociclib and palbociclib share structural similarities, abemaciclib differs, which may contribute to differences in liver toxicity risk (10). Successful treatment transitions from ribociclib to palbociclib or abemaciclib have been reported previously (11). Based on these findings, we hypothesized that cross-reactivity between abemaciclib and palbociclib is low, making the switch a feasible and effective strategy. A comprehensive analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS) database assessed the risk of drug-induced liver injury (DILI) associated with CDK4/6 inhibitors (abemaciclib, ribociclib, and palbociclib). The study identified a positive signal for DILI with ribociclib [reporting odds ratio (ROR)=2.60] and abemaciclib (ROR=2.37) (12). Our findings suggest that switching from abemaciclib to palbociclib reduces the risk of liver dysfunction, as no cases of relapse were observed after the switch, and patients remained clinically stable. For causality assessment in suspected DILI, the revised Roussel Uclaf Causality Assessment Method (RUCAM) is widely applied.

In Japan, the Revised Electronic Causality Assessment Method for Japan 2023 (RECAM-J 2023) was developed as an adaptation of RUCAM for routine clinical practice (13). This scale has been validated and demonstrated clinical utility. In our analysis, RECAM-J 2023 scores for abemaciclib were ≥ 8 (highly probable) in all cases, supporting abemaciclib as the causative agent. In contrast, endocrine therapies (letrozole, fulvestrant, tamoxifen, or anastrozole) scored between -3 and 3, indicating only a possible association (Table I). Users should be aware of certain precautions when applying the RECAM-J 2023 score. First, care must be taken to correctly identify the suspected causative drug and avoid selection errors. Second, it is necessary to accurately collect patient information regarding liver function impairment and properly incorporate it into the scoring. The RECAM-J 2023 score should be used with a full understanding of these limitations.

This study has several strengths. We employed a validated DILI assessment tool to identify the causative agent and provided real-world evidence supporting the feasibility of switching CDK4/6 inhibitors in clinical practice. Given the scarcity of published reports on such transitions, our findings add clinically relevant insights to the existing literature.

Conclusion

The RECAM-J 2023 offers a reliable and validated method for identifying DILI in routine clinical practice in Japan. By

accurately determining the causative drug, this tool can support safer rechallenge and continuation of CDK4/6 inhibitor therapy, thereby helping optimize treatment strategies for patients who develop CDK4/6 inhibitor-induced hepatotoxicity.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

ST, KU, and KW confirmed the medical assessments and designed the study. KU and TK provided advice regarding the statistical analyses. ST and KU performed the statistical analyses. ST, KW, and KU drafted and edited the manuscript. All the Authors discussed the results and contributed to the final version of the manuscript.

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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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