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ORIGINAL RESEARCH

Adjuvant abemaciclib in early-stage breast cancer: hypothesis-generating safety observations from a real-world cohort study

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Abstract

Background: Invasive disease-free survival in adjuvant treatment of HR$^+$/HER2$^-$ early-stage breast cancer is improved by the use of CDK4/6 inhibitors. However, to date, minimal data are available on their safety and effectiveness in older patients (≥70 years old).

Methods: A retrospective, multi-centre cohort study was conducted in two oncology centres in Pavia, Italy. Patients had to have received at least 3 months of therapy with adjuvant abemaciclib (a CDK4/6 inhibitor). Data on demographics, toxicity, dose reductions and clinical outcomes were analysed. Analyses were descriptive, with continuous variables reported as median (IQR) and categorical variables as counts and percentages.

Results: Fifty-four patient records were reviewed (median age 55; six patients ≥70 years (older-age subgroup). Adverse events of any grade were reported in 53/54 patients (98.1%), most commonly haematological and gastrointestinal. Dose reductions occurred more frequently and earlier in the older-age subgroup (66.7% *versus* 45.8%; median 4.2 *versus* 8.3 months). Toxicities were generally of low–moderate grade and manageable.

Conclusion: During adjuvant abemaciclib, low–moderate-grade toxicities were common, particularly haematological and gastrointestinal events. Older patients showed a numerically higher rate of dose reductions, suggesting a potential need for personalized dosing and early monitoring in this subgroup. These findings should be considered hypothesis-generating and warrant confirmation in larger prospective studies.

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Keywords: abemaciclib, CDK 4/6 inhibitors, older people, quality of life, toxicity.

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Introduction

Breast cancer is the leading tumour diagnosed in women, and current evidence points to an increased prevalence in older patients (≥70 years) with a higher mortality due to immunosenescence, diagnostic delay and under-treatment.[1,2] Additionally, older patients remain underrepresented in clinical trials, and the primary guidelines for treating this population are based on studies mainly conducted on younger groups. Specifically, these guidelines often fail to account for the considerable

variability amongst older adults, including their comorbidities, performance status, physiological age and frailty.[3]

Endocrine therapy is the first-choice treatment for patients with hormone receptor-positive (HR^+) metastatic breast cancer (MBC), although half of these patients become resistant to endocrine therapy over time. The highly selective inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6), including palbociclib, ribociclib and abemaciclib, are effective in circumventing resistance to hormone therapy, restoring hormone sensitivity and delaying the need for chemotherapeutic agents. Therefore, CDK4/6 inhibitors combined with hormone therapy have changed the history of MBC, and palbociclib, abemaciclib and ribociclib are currently the three main FDA-approved CDK4/6 inhibitors for the treatment of HR^+ and human epidermal growth factor receptor 2-negative ($HER2^-$) advanced MBC.[4,5] The older population is underrepresented in clinical trials of MBC treated with CDK4/6 inhibitors. Additionally, when enrolled, all participants have an Eastern Cooperative Oncology Group (ECOG) functional status of 0–1.[6] However, real-world data indicate that CDK4/6 inhibitors with endocrine therapy are well tolerated in advanced $HR^+/HER2^-$ breast cancer, regardless of patient age: the Hellenic Cooperative Oncology Group (HeCOG) included 365 patients with MBC treated with ribociclib or palbociclib combined with hormonal therapy; in patients aged ≥75 years (n=43, 11.9%), adverse events were observed in a similar proportion as in the overall population, with just over half experiencing at least one toxicity.[7]

Similarly, invasive disease-free survival and distant recurrences in adjuvant treatment of $HR^+/HER2^-$ early-stage breast cancer are improved by CDK4/6 inhibitors. However, data on the safety and efficacy of CDK4/6 inhibitors in older patients are limited. A recent meta-analysis showed that the invasive disease-free survival benefit was observed irrespective of menopausal status, Ki-67 index, tumour grade, and previous chemotherapy.[8] In the adjuvant setting, the aspect of toxicity in the older women is even more important.

This study aims to enhance our comprehension of the clinical efficacy and safety of adjuvant abemaciclib in older women in a real-world setting compared with younger women.

Methods

Study design and setting

This is a retrospective, multicentre cohort study including patients with $HR^+/HER2^-$ early-stage breast cancer who received adjuvant abemaciclib due to a high risk of recurrence. Eligible patients were treated between August 2022 and February 2025 in two oncology centres, Policlinico San Matteo (PSM) and Istituti Clinici Scientifici Maugeri (ICSM), located in Pavia, Northern Italy. Both institutions are university-affiliated hospitals that typically manage over 150 new breast cancer cases annually. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research[9] and received approval from the local Ethics Committee (Comitato Etico Area Pavia) and the Institutional Review Board (approval number: P-0014317/25). Written informed consent was obtained from all participants.

The exploratory hypothesis of this study was that older patients (≥70 years) might experience a higher incidence of treatment-related toxicities and dose reductions compared with younger patients.

Data collection

Clinical data were extracted from hospital medical records and included patient demographics, the Cumulative Illness Rating Scale (CIRS) score, treatment characteristics, dose modifications or interruptions, and the occurrence of toxicities of any grade. We collected adverse drug reactions according to the Common Terminology Criteria Adverse Events v5.0.[10] Inclusion criteria were as follows: (1) age ≥18 years, regardless of sex; (2) receipt of at least 3 months of adjuvant abemaciclib; and (3) provision of written informed consent. Patients with incomplete baseline characteristics or insufficient follow-up data were excluded from the analysis.

Statistical analysis

Given the small sample size, especially in the older subgroup (≥70 years), analyses were primarily descriptive and exploratory. Continuous variables were summarized as median and interquartile range (IQR). Categorical variables were presented as counts and percentages. No formal hypothesis testing or inferential analyses were performed to avoid overinterpretation of limited data. Descriptive comparisons between age subgroups are presented solely to illustrate observed differences in this dataset and should be interpreted cautiously. Observation time began at adjuvant abemaciclib initiation and ended at toxicity, dose reduction, or the last available follow-up in case of censoring.

Results

Characteristics of the study population

Fifty-four patient records were retrospectively reviewed, with a median age of 55 years (IQR 49–62). Six (11.1%) patients were aged ≥70 years (older subgroup), whilst 48 (88.9%) patients were younger than 70 years (younger subgroup). The median age was 75 years (IQR 73–78) in the older subgroup and 54 years (IQR 48–59) in the younger

subgroup. Comorbidity burden was higher in the older subgroup, though not statistically tested due to small numbers (median CIRS severity index 1.23 *versus* 1.00; median CIRS comorbidity index 0.50 *versus* 0.00). The most frequent comorbid conditions in the older subgroup were cardiovascular diseases (100%), hypertension (66.6%) and endocrine-metabolic disorders (50%). Baseline clinical and pathological characteristics are summarized in Table 1.

Incidence and timing of toxicity

Adverse events of any grade were reported in 53 out of 54 patients (98.1%), most commonly haematological and gastrointestinal events (Table 2). In the older subgroup, all patients (6/6) experienced at least one adverse event, whilst in the younger group, 47 of 48 patients (97.9%) did so. Median time-to-first toxicity was 4.2 months in the older subgroup and 3.8 months in the younger group.

Dose reductions

Globally, 26 (48.2%) patients required at least one dose reduction. Dose reductions were observed more frequently and earlier in the older subgroup (66.7% *versus* 45.8%; median time 4.2 *versus* 8.3 months). Because of the small number of older patients, no hazard ratios or formal inferential statistics are reported for this outcome.

Types of toxicities

Table 2 synthesizes all the toxicities and their severity listed later.

Haematological

At least one haematological toxicity was observed in 83.3% of older patients and 68.8% of younger patients. Neutropenia was the most common event (66.7% overall), whilst febrile neutropenia was rare (1.9%). Anaemia and thrombocytopenia were mostly low grade.

Gastrointestinal

Diarrhoea occurred in 87% of patients, mostly grade 1–2. Nausea affected 18.5% of patients, with no grade ≥3 events.

Hepatic and renal

ALT and AST elevations were reported in 9.3% of patients, ALP in 7.4%, and creatinine in 3.7%, all low grade.

Cardiopulmonary

No QTc prolongation or interstitial lung disease was observed.

Overall, adverse events were mostly of low–moderate grade and clinically manageable.

Discussion

This real-world retrospective analysis assessed the safety and tolerability profile of adjuvant abemaciclib in patients with HR$^+$ early-stage breast cancer. Adverse events of any grade occurred in 98.1% of patients, with haematological and gastrointestinal toxicities being the most frequently observed.

Neutropenia was the most common haematological toxicity, affecting two-thirds of the cohort, although febrile neutropenia was rare (1.9%). These findings are consistent with safety data from phase III trials of CDK4/6 inhibitors in the adjuvant setting, such as monarchE, PALLAS and NATALEE, where neutropenia was frequently observed but rarely complicated by infection.[11–14] Anaemia and thrombocytopenia were less common and predominantly of low grade according to recent data.[15]

Gastrointestinal events, particularly diarrhoea, were frequently reported, with the majority of cases being grade 1 or 2. Only one patient experienced grade 3 diarrhoea. These observations are comparable to previous studies involving abemaciclib and ribociclib, where diarrhoea is a well-documented class effect.[11–15] These adverse events can be mechanistically linked to the selective inhibition of CDK4/6 by abemaciclib. By blocking CDK4/6, abemaciclib prevents phosphorylation of the retinoblastoma protein, leading to G1 cell-cycle arrest in proliferating cells. Whilst this effect is therapeutic in tumour cells, it also affects normal proliferating cells, such as haematopoietic progenitors in the bone marrow, resulting in cytopenias, and epithelial cells of the gastrointestinal tract, causing diarrhoea. The continuous dosing schedule of abemaciclib may further contribute to cumulative toxicity.[16] These mechanistic insights help explain the observed early onset and frequency of adverse events, particularly in patients with reduced physiological reserve, such as those in the older subgroup. Liver enzyme elevations and creatinine increases were infrequent and mild in severity, whilst no cardiopulmonary toxicities, including QTc prolongation or interstitial lung disease, were observed.

Almost half of the patients (48.2%) required a dose reduction, and notably, almost all older patients underwent dose adjustments, compared with younger individuals, suggesting a higher vulnerability to treatment-related toxicities in this subgroup. Our data are consistent with other papers. For example, an American retrospective cohort compared toxicity profiles between adjuvant (n≈30) and metastatic patients treated with abemaciclib between March 2018 and September 2021. Amongst adjuvant patients, 100% experienced adverse events, with 12.5% encountering G3 events and 18.8% discontinuing treatment due to toxicity.[17] In a recent Japanese

Table 1. Baseline characteristics of enrolled patients.

Characteristics	Patients (*n*, %)	Elderly (*n*=6)	Young (*n*=48)
Age at diagnosis (years), median (IQR)	55 (49–62)	75 (73–78)	54 (48–59)
Histology, *n* (%)			
Ductal	39 (72%)	6 (100%)	33 (69%)
Lobular	12 (22%)	0 (0%)	12 (25%)
Mixed ductal and lobular	3 (6%)	0 (0%)	3 (6%)
Oestrogen receptor status (primary), *n* (%)			
<1%	0	0	0
1–9%	0	0	0
10%	0	0	0
>10%	54 (100%)	6 (100%)	48 (100%)
Progesterone receptor status (primary), *n* (%)			
<1%	4 (7.4%)	1 (16.7%)	3 (6.3%)
>1%	50 (92.6%)	5 (83.3%)	45 (93.7%)
HER2 receptor status (primary), *n* (%)			
0	26 (48%)	3 (50%)	23 (47.9%)
1+	15 (28%)	1 (16.7%)	14 (29.2%)
2+ (ISH negative)	13 (24%)	2 (33.3%)	11 (22.9%)
Grade primary, *n* (%)			
G1	0	0	0
G2	22 (41%)	1 (17%)	21 (44%)
G3	32 (59%)	5 (83%)	27 (56%)
Pathological T category, *n* (%)			
T1c	13 (24%)	1 (16.7%)	12 (25%)
T2	28 (52%)	5 (83.3%)	23 (47.9%)
T3	13 (24%)	0	13 (27.1%)
T4	0	0	0
Pathological N category, *n* (%)			
N1	21 (39%)	3 (50%)	18 (37.5%)
N2	21 (39%)	1 (16.7%)	20 (41.7%)
N3	12 (22%)	2 (33.3%)	10 (20.8%)
Management of primary tumour, *n* (%)			
Upfront surgery	44 (81.5%)	5 (83.3%)	39 (81.3%)
Neoadjuvant chemotherapy	10 (18.5%)	1 (16.7%)	9 (18.8%)
Neoadjuvant endocrine therapy	0	0	0
Adjuvant treatment, *n* (%)			
Endocrine therapy	13 (24.1%)	1 (16.7%)	12 (25%)
Chemotherapy	0	0	0
Both	41 (75.9%)	5 (83.3%)	36 (75%)

Table 2. Summary of adverse events and dose reductions (*n*=54).

Toxicity	Patients affected, *n* (%)	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	53 (98.15%)	–	–	–	–
Haematological toxicities					
Neutropenia	36 (66.67%)	11 (20.37%)	11 (20.37%)	13 (24.07%)	1 (1.85%)
Febrile neutropenia	1 (1.85%)	–	–	–	–
Anaemia	11 (20.37%)	11 (20.37%)	0	0	0
Thrombocytopenia	5 (9.26%)	4 (7.41%)	0	1 (1.85%)	0
Gastrointestinal toxicities					
Diarrhoea	47 (87.04%)	26 (48.15%)	20 (37.04%)	1 (1.85%)	0
Nausea	10 (18.52%)	7 (12.96%)	3 (5.56%)	0	0
Hepatic and renal toxicities					
ALT elevation	5 (9.26%)	4 (7.41%)	1 (1.85%)	0	0
AST elevation	5 (9.26%)	4 (7.41%)	1 (1.85%)	0	0
ALP elevation	4 (7.41%)	4 (7.41%)	0	0	0
Creatinine elevation	2 (3.70%)	1 (1.85%)	1 (1.85%)	0	0
Cardiopulmonary toxicities					
QTc prolongation	0 (0%)	–	–	–	–
Interstitial lung disease	0 (0%)	–	–	–	–
Dose reductions	26 (48.15%)	–	–	–	–

study, a total of 42% of patients required at least one abemaciclib dose reduction.[18]

Although the sample size of older patients was small, this finding is in line with other real-world data indicating increased susceptibility amongst older adults to CDK4/6 inhibitor-related toxicity. Dose reductions occurred more frequently and earlier in older patients, suggesting that age-related factors may contribute to decreased treatment tolerance. These factors include a higher burden of comorbidities, reduced functional reserve across multiple organ systems, diminished physiological stress resilience, and potentially limited cognitive or social resources. Moreover, earlier dose reductions in older patients likely reflect greater clinical caution, as clinicians tend to adjust treatment sooner at the first signs of toxicity in this population. Importantly, chronological age alone may not fully capture an individual's vulnerability, as functional capacity and overall health status can vary widely amongst older adults.[19] However, given the small number of older patients, this study was not powered to formally dissect these relationships.

Building on experiences with other targeted therapies, which suggest that initial dose escalation may reduce toxicity and treatment discontinuation, a dose-escalation strategy for adjuvant abemaciclib is currently under investigation. The results of the TRADE trial were recently presented at the ASCO 2025 Annual Meeting. The primary endpoint was met: a greater proportion of patients (70.8%) were able to reach and maintain the full 150 mg dose at 12 weeks compared to those in the monarchE trial. Early treatment discontinuation was uncommon, with 93.3% of patients still receiving therapy at 12 weeks. A lower incidence and severity of clinically significant and common toxicities, such as diarrhoea, were also reported.[20]

Due to the limited duration of follow-up in this real-world cohort, it is currently not possible to provide meaningful data on treatment efficacy or long-term clinical outcomes. Corti et al.[21] have recently evaluated the mechanisms underlying resistance to adjuvant abemaciclib by integrating clinicopathological data with comprehensive genomic profiling of tumours. This study highlights the need for predictive biomarkers to personalize adjuvant

therapy by tailoring treatment choices based on tumour genomics and patient-specific risk profiles.

The introduction of abemaciclib in the adjuvant setting also raises important economic considerations. Treatment with abemaciclib over a 2-year period involves high costs, related both to the price of the drug and to indirect expenses such as clinical monitoring, management of adverse events and potential loss of workdays. These costs may contribute to financial toxicity, with relevant clinical consequences, including reduced adherence, delays in treatment initiation or early discontinuation. Moreover, the economic impact can compromise patients' quality of life and psychosocial well-being. From a sustainability perspective, it is essential to assess the appropriateness of the indication and the cost-effectiveness of the treatment in selected populations, and to implement tools for assessing financial toxicity within both clinical practice and clinical trials.

Clinical decision-making for the use of adjuvant CDK4/6 inhibitors should be guided by a combination of tumour-related risk factors and patient-specific characteristics, including comorbidities, functional status and anticipated adherence to therapy. Whilst abemaciclib is the approved agent in this setting, ribociclib may also be considered in selected cases; however, its use requires careful monitoring due to a higher risk of cardiological adverse events, particularly QTc prolongation, which may be especially relevant in older patients or those with pre-existing cardiovascular conditions.[22] In patients aged ≥70 years, treatment decisions must be individualized, weighing potential clinical benefit against the risk of adverse events and impact on quality of life. These considerations underscore the importance of a tailored approach when offering adjuvant CDK4/6 inhibitors to older adults.

This study is subject to several limitations. First, the retrospective nature introduces a risk of information bias. This affects underreporting or misclassification of adverse events, especially lower-grade or subjective ones like fatigue or nausea. These may not have been systematically recorded in medical records. Second, the absence of centralized adverse event grading or prospective toxicity assessment introduces observer bias, and toxicity attribution may vary amongst clinicians. Third, the relatively small sample size (n=54), and especially the low number of older patients (n=6), limit the generalizability of observations. This also precludes formal comparisons between age subgroups. Whilst a numerically higher rate of dose reduction was observed in older patients, this finding should be interpreted with caution due to the small older cohort. Selection bias may have occurred as patients included were already selected for adjuvant endocrine therapy and abemaciclib. This possibly excludes those unfit for this treatment due to comorbidities or poor performance status. As a result, the safety profile observed may not fully represent more frail or vulnerable patient populations. Additionally, adherence, patient-reported outcomes and long-term efficacy were not assessed.

Despite these limitations, the study reflects routine clinical practice and includes a broader patient population than that typically enrolled in clinical trials, offering valuable insights into toxicity profiles in a real-world setting. Moreover, the study highlights a clinically relevant difference in treatment tolerability by age, showing a significantly higher incidence of dose reduction amongst older patients. This age-based analysis provides preliminary evidence to support the need for age-tailored toxicity monitoring and management strategies in the adjuvant setting.

Conclusions

In conclusion, during adjuvant abemaciclib, low–moderate-grade toxicities were common, particularly haematological and gastrointestinal events. Older patients showed a numerically higher rate of dose reductions, suggesting a potential need for personalized dosing and early monitoring in this subgroup. These findings should be considered hypothesis-generating and warrant confirmation in larger prospective studies.

Contributions: Conception and design: AL and FS. Collection and assembly of data: AL, SF, GC, GG. Data analysis and interpretation: GG and CK. Manuscript writing: all authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. The authors decline the use of artificial intelligence, language models, machine learning, or similar technologies to create content or assist with writing or editing of the manuscript.

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