



Research Article

Neutropenia Requiring Ribociclib Dose Modification in Metastatic Breast Cancer: A Prospective Observational Cohort Study in Peshawar, Pakistan.

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Abstract: **Background:** Ribociclib is an established cyclin-dependent kinase 4/6 inhibitor used with endocrine therapy for hormone receptor-positive, HER2-negative metastatic breast cancer. Neutropenia is a clinically important hematologic adverse event that may require treatment modification. **Objective:** To determine the frequency of neutropenia requiring ribociclib dose modification among patients with metastatic breast cancer in Peshawar, Pakistan. **Methods:** This single-center prospective observational cohort study was conducted at Hayatabad Medical Complex, Peshawar, Pakistan, from January to September 2023. Of 110 eligible women with hormone receptor-positive, HER2-negative metastatic breast cancer, 95 consented and were enrolled at initiation of ribociclib as part of routine clinical care. Twelve were lost to follow-up; 83 completed follow-up and were analyzed. Repeated complete blood counts were used to monitor neutropenia according to Common Terminology Criteria for Adverse Events (CTCAE) thresholds. The primary outcome was neutropenia prompting temporary treatment interruption and/or dose reduction. Pearson's chi-square tests evaluated associations with baseline factors. **Results:** Of the 83 women analyzed, the mean age was 35.80 ± 9.64 years and mean body mass index was 25.00 ± 1.97 kg/m². Neutropenia requiring treatment interruption and/or dose reduction was recorded in 40 participants (48.2%). No statistically significant associations were observed with age group ($p = 0.215$), socioeconomic class ($p = 0.614$), residence ($p = 0.487$), education ($p = 0.221$), occupational status ($p = 0.995$), family history ($p = 0.106$), body mass index category ($p = 0.614$), or disease duration ($p = 0.794$). **Conclusion:** Neutropenia requiring ribociclib treatment interruption and/or dose reduction occurred in 48.2% of the analyzed cohort. These findings describe a composite treatment-modification outcome rather than the incidence of neutropenia of any grade; larger studies with complete follow-up and separate event categories are needed.

Keywords: ribociclib; neutropenia; metastatic breast cancer; CDK4/6 inhibitors; dose modification.

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INTRODUCTION

Metastatic breast cancer remains a major therapeutic challenge despite improvements in treatment outcomes. Advanced disease requires sustained systemic therapy, and the cumulative burden of treatment-related adverse effects can affect its delivery. Studies of metastatic breast cancer emphasize the importance of individualized treatment and toxicity assessment (Westphal et al.; Marino et al.; Jin and Mu).

Breast cancer is a major public-health concern in Pakistan. A national cancer-registry report covering 2015–2019 documented the substantial burden of breast cancer among Pakistani women (Ikram et al.).

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have transformed the management of hormone receptor-positive, HER2-negative advanced breast cancer. Commonly used agents include palbociclib, ribociclib, and abemaciclib. Hematologic toxicities, particularly neutropenia and leukopenia, are frequently reported with this class, although adverse-event profiles differ across agents. In pooled safety analyses, neutropenia was common during palbociclib therapy, while abemaciclib showed a comparatively different toxicity profile (Thill and Schmidt; Diéras et al.; Rugo et al.; Pu et al.).

Ribociclib is used with endocrine therapy for hormone receptor-positive, HER2-negative advanced breast cancer (Cersosimo). In a pooled analysis of the MONALEESA-2, -3, and -7 trials, neutropenia was a frequent adverse event and an important reason for treatment modification; trial analyses suggested that protocol-directed dose reductions did not diminish treatment benefit (Burris et al.). A Danish real-world study also documented frequent dose adjustments during ribociclib therapy (Kristensen et al.). CDK4/6 inhibitor-associated neutropenia is generally associated with reversible cell-cycle arrest rather than the cytotoxic mechanism seen with traditional chemotherapy (Thill and Schmidt). The MONALEESA-2 survival analysis further established the clinical relevance of ribociclib in advanced breast cancer (Hortobagyi et al.). The subsequent NATALEE trial extended investigation of ribociclib to the early breast cancer setting (Slamon et al.).

Recent South Asian reports provide additional context. A prospective Indian study described neutropenia and treatment modification among patients treated with CDK4/6 inhibitors (Sreenath et al.). A 2024 retrospective study from eastern India documented grade 1–3 neutropenia in a cohort of 24 patients treated with CDK4/6 inhibitors, including 15 who received ribociclib (Das Majumdar et al.). These findings underscore the importance of regional safety data, while differences in study populations, adverse-event definitions, and outcomes require careful interpretation.

Local data describing neutropenia specifically associated with ribociclib dose modification remain limited. This study therefore assessed the frequency of the composite outcome—neutropenia requiring dose interruption or reduction—and its association with selected baseline characteristics in women with metastatic breast cancer treated at a tertiary oncology center in Peshawar, Pakistan.

MATERIALS AND METHODS

Study Design and Setting

This single-center prospective observational cohort study was conducted in the Department of Medical Oncology, Hayatabad Medical Complex, Peshawar, Pakistan, between January and September 2023, following approval by the hospital's institutional review board. Participants were recruited at the initiation of clinician-prescribed ribociclib therapy as part of routine clinical care, and were prospectively followed through repeated hematological assessments during subsequent treatment cycles. Treatment allocation was not determined by the investigators.

Participants

Eligible participants were women aged 20–60 years with hormone receptor-positive, HER2-negative metastatic (stage IV, M1) breast cancer of at least three months' duration, diagnosed from clinical, radiologic, and histopathologic findings. Non-probability consecutive sampling was used. Pregnant women and patients with contraindications to ribociclib, chronic kidney disease, liver cirrhosis, or ischemic heart disease were excluded. The intended final analyzable sample size was 83, estimated using a previously reported 7% frequency of grade 4 neutropenia, a 95% confidence level, and a 5.5% margin of error with the WHO sample-size calculator (Kristensen et al.). Among 110 eligible patients, 15 did not provide consent; 95 consented and were enrolled, of whom 12 were lost during follow-up. The final analysis therefore included 83 participants who completed follow-up. Written informed consent was obtained from all enrolled participants.

Study Procedures and Outcome

Baseline clinical history, examination findings, and investigations, including a complete blood count (CBC), were documented at treatment initiation. Ribociclib was prescribed with endocrine therapy as part of routine clinical care. CBC with differential was repeated at two-week intervals during the first two cycles and monthly during the next four cycles; further testing intervals were determined by the treating clinician according to the clinical protocol. Neutropenia was classified using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) based on absolute neutrophil count (ANC). The thresholds corresponding to CTCAE grading used during the 2023 study period were grade 1: ANC below the laboratory lower limit of normal but $\geq 1,500$ cells/ μL ; grade 2: 1,000 to $<1,500$ cells/ μL ; grade 3: 500 to $<1,000$ cells/ μL ; and grade 4: <500 cells/ μL (National Cancer Institute). The primary outcome was neutropenia requiring ribociclib dose modification, defined as either temporary treatment interruption or dose reduction because of neutropenia during follow-up. Patients who experienced both types of modification were counted once in this composite outcome. Counts of interruptions and reductions separately, as well as neutropenia episodes without modification, were not available in the supplied aggregate dataset. Age, anthropometry, disease duration, socioeconomic class, residence, education (illiterate, primary, or secondary and above), occupational status, and family history of breast cancer were recorded on a structured pro forma.

Statistical Analysis

Data were entered and analyzed using SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables (age, height, weight, body mass index, and duration of disease) were summarized as mean $\pm$ standard deviation. Categorical variables were summarized as frequency and percentage. Pearson's chi-square test without continuity correction was used to compare the frequency of neutropenia requiring dose modification across categories of baseline variables. A two-sided p-value ≤ 0.05 was considered statistically significant. The analyses were based on the available categorical records.

RESULTS

Of 110 eligible women, 15 did not provide consent and 95 were enrolled. Twelve of the 95 enrolled participants (12.6%) were lost during follow-up, leaving 83 women (87.4% of enrolled participants) who completed follow-up and were included in the final analysis (Figure 1).

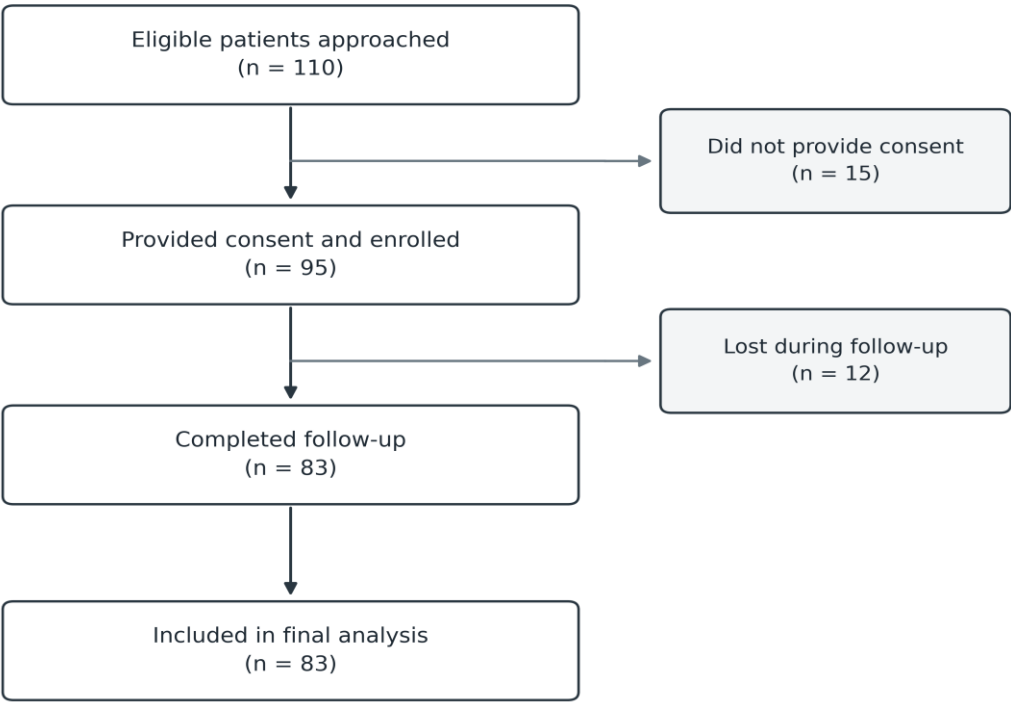


Figure 1. Flowchart of participant eligibility, consent, follow-up, and inclusion in the final analysis.

Among the 83 women analyzed, mean age was 35.80 ± 9.64 years (range, 20–58 years); 65 participants (78.3%) were aged 20–40 years and 18 (21.7%) were aged 41–60 years. Mean height was 5.54 ± 0.07 ft, mean weight was 69.22 ± 5.44 kg, mean body mass index was 25.00 ± 1.97 kg/m², and mean duration of disease was 4.19 ± 1.55 years (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics of Participants Included in the Analysis (N = 83)

Characteristic	Value
Age, years, mean $\pm$ SD (range)	35.80 $\pm$ 9.64 (20–58)
20–40 years, n (%)	65 (78.3)
41–60 years, n (%)	18 (21.7)
Height, ft, mean $\pm$ SD	5.54 $\pm$ 0.07
Weight, kg, mean $\pm$ SD	69.22 $\pm$ 5.44
Body mass index, kg/m ² , mean $\pm$ SD	25.00 $\pm$ 1.97
Duration of disease, years, mean $\pm$ SD	4.19 $\pm$ 1.55
Socioeconomic class, n (%)	
Poor	36 (43.4)
Middle class	29 (34.9)
Rich	18 (21.7)
Residence, n (%)	
Rural	59 (71.1)
Urban	24 (28.9)
Educational status, n (%)	
Illiterate	45 (54.2)
Primary	25 (30.1)
Secondary and above	13 (15.7)
Occupational status, n (%)	
Employed	56 (67.5)
Housewife	27 (32.5)
Family history of breast cancer, n (%)	51 (61.4)
Neutropenia with dose modification, n (%)	40 (48.2)

SD, standard deviation. Education groups are mutually exclusive: illiterate, primary, and secondary and above.

The baseline socioeconomic groups were recorded as poor in 36 (43.4%) participants, middle in 29 (34.9%), and rich in 18 (21.7%). Fifty-nine (71.1%) participants lived in rural areas. Educational attainment was categorized as illiterate for 45 (54.2%), primary for 25 (30.1%), and secondary and above for 13 (15.7%). Fifty-six participants (67.5%) were employed and 27 (32.5%) were housewives. A family history of breast cancer was recorded in 51 (61.4%) participants (Table 1).

During prospective follow-up, neutropenia requiring temporary ribociclib interruption and/or dose reduction occurred in 40 of 83 analyzed women (48.2%). The remaining 43 participants (51.8%) did not meet this composite endpoint. Their classification does not establish whether or not they experienced neutropenia that did not require treatment modification. The aggregate data did not distinguish the separate numbers of interruptions and dose reductions.

In stratified analyses, the composite outcome did not differ significantly across the examined baseline variables (Table 2): age group ($p = 0.215$), socioeconomic class ($p = 0.614$), residence ($p = 0.487$), educational category ($p = 0.221$), occupational status ($p = 0.995$), family history of breast cancer ($p = 0.106$), body mass index category ($p = 0.614$), or duration of disease ($p = 0.794$). All comparisons used Pearson’s chi-square test.

Table 2. Neutropenia Requiring Ribociclib Treatment Interruption and/or Dose Reduction by Baseline Characteristic (N = 83)

Characteristic	Neutropenia requiring dose modification, n (%)	No composite outcome, n (%)	χ^2 (df)	p-value
Age group				
20–40 years	29 (44.6)	36 (55.4)	1.54 (1)	0.215
41–60 years	11 (61.1)	7 (38.9)		
Socioeconomic class				
Poor	18 (50.0)	18 (50.0)	0.98 (2)	0.614
Middle class	12 (41.4)	17 (58.6)		
Rich	10 (55.6)	8 (44.4)		
Residence				
Rural	27 (45.8)	32 (54.2)	0.48 (1)	0.487
Urban	13 (54.2)	11 (45.8)		
Educational status				
Illiterate	21 (46.7)	24 (53.3)	3.02 (2)	0.221
Primary	10 (40.0)	15 (60.0)		
Secondary and above	9 (69.2)	4 (30.8)		
Occupational status				
Employed	27 (48.2)	29 (51.8)	0.00 (1)	0.995
Housewife	13 (48.1)	14 (51.9)		
Family history of breast cancer				
Yes	21 (41.2)	30 (58.8)	2.61 (1)	0.106
No	19 (59.4)	13 (40.6)		
Body mass index				
$\leq 25 \text{ kg/m}^2$	22 (45.8)	26 (54.2)	0.25 (1)	0.614
$> 25 \text{ kg/m}^2$	18 (51.4)	17 (48.6)		
Duration of disease				
≤ 3 years	16 (50.0)	16 (50.0)	0.07 (1)	0.794
> 3 years	24 (47.1)	27 (52.9)		
Overall	40 (48.2)	43 (51.8)	—	—

Values are n (row %) unless otherwise indicated. Pearson's chi-square tests without continuity correction were used; df, degrees of freedom. "No composite outcome" means no neutropenia requiring treatment interruption or dose reduction; it does not necessarily mean an absence of neutropenia. Educational groups are mutually exclusive.

DISCUSSION

In this single-center prospective observational cohort study, 40 of the 83 analyzed women (48.2%) with hormone receptor-positive, HER2-negative metastatic breast cancer developed neutropenia that prompted temporary treatment interruption and/or ribociclib dose reduction. This was a composite outcome measured during clinical follow-up, not the incidence of neutropenia of any grade and not the frequency of dose reduction alone. Pooled MONALEESA analyses have documented neutropenia as an important reason for treatment changes (Burris et al.), while a Danish observational series reported ribociclib dose adjustments among patients with metastatic breast cancer (Kristensen et al.). Because the event definitions and follow-up durations differ, direct comparison of proportions should be interpreted cautiously.

CDK4/6 inhibitor-related neutropenia is described as predominantly reversible and mechanistically distinct from chemotherapy-associated myelosuppression (Thill and Schmidt). Pooled MONALEESA trial findings and subsequent observational reports indicate that dose modification does not necessarily imply loss of efficacy (Burris et al.; Kristensen et al.). However, the present study did not measure treatment response, progression-free survival, or overall survival. Consequently, it cannot independently establish whether the dose changes observed had any effect on treatment efficacy. No statistically significant association was found between the composite outcome and the baseline characteristics examined (all $p > 0.05$). Nevertheless, a non-significant test result should not be interpreted as evidence that a predictor has no effect. With 83 participants, the study may have had limited ability to identify modest associations; the findings also reflect the particular categories selected for analysis.

Other studies have examined factors beyond the demographic characteristics available here. One observational analysis of palbociclib-associated neutropenia considered baseline neutrophil count and other clinical predictors (Lavery et al.). A separate study reported that febrile neutropenia was uncommon in patients with palbociclib-associated high-grade neutropenia (Ivey et al.). A pharmacist-led monitoring study highlighted the role of structured blood-count surveillance in identifying hematologic adverse events and reducing treatment delays (De Raya and Modlin). Supportive-care guidelines provide additional context for managing treatment-related hematologic toxicity (Griffiths et al.). The applicability of these external observations to ribociclib use in the present Pakistani cohort should be assessed cautiously.

Several limitations warrant consideration. The study was conducted at a single center using non-probability consecutive sampling, and the analyzed cohort was modest in size, which limits generalizability and statistical precision. Twelve of 95 enrolled patients (12.6%) were lost during follow-up; because their outcomes are not available, complete-case analysis may introduce attrition bias if their likelihood of neutropenia differed from that of retained participants. The primary outcome combined neutropenia-related temporary treatment interruptions and dose reductions, without separate event counts, episode frequency, ANC grade distribution, or counts of neutropenia not requiring modification. As a result, the data cannot establish the overall incidence of any-grade neutropenia or grade-specific event rates. Baseline ANC, patient-level follow-up duration, and progression-free and overall survival outcomes were not provided. The exact CTCAE version should be verified against the ethics-approved local protocol; the ANC cutoffs reproduced here follow the CTCAE framework applicable during 2023.

Despite these limitations, the study provides locally relevant observations on neutropenia-associated treatment modification during routine ribociclib therapy in Peshawar. Future multicenter prospective investigations should report complete participant disposition, neutropenia grades, temporary interruptions and dose reductions separately, and clinical outcomes associated with dose changes.

CONCLUSION

In this single-center prospective observational cohort, neutropenia requiring temporary interruption and/or dose reduction of ribociclib occurred in 40 of 83 women included in the final analysis (48.2%). None of the eight examined baseline factors showed a statistically significant association with this composite endpoint. Interpretation is limited by sample size, loss to follow-up, and the absence of separate counts for neutropenia grade, interruption, and dose reduction. Larger prospective multicenter studies are warranted.

Declarations

Ethical approval: The study was approved by the Institutional Review Board (IRB) of Hayatabad Medical Complex, Peshawar, Pakistan, before the commencement of participant recruitment and data collection. All study procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ribociclib treatment was prescribed as part of

routine clinical care, and treatment decisions were made by the attending physicians. Participants' privacy and confidentiality were respected throughout the study, and findings were reported in an aggregated manner without disclosing personally identifiable information.

Informed consent: Written informed consent was obtained from the 95 women who enrolled; 15 eligible women did not consent and were excluded.

Competing interests: The authors declare that they have no competing interests.

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