Real-World Safety Profile of Generic Palbociclib in Hormone Receptor–Positive, HER2-Negative Metastatic Breast Cancer: A Prospective Observational Study in Iraq"

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Abstract: *Background*: Breast cancer accounts for the highest incidence of cancer among Iraqi women. Generic Palbociclib has recently become available, yet there remains a lack of real-world clinical equivalence data.

Methods: A prospective observational study carried out between September 2024 & April 2025 at the oncology teaching hospital in the medical city complex with (175) participants included those on generic palbciclib with fluvestrant or Aromatase inhibitor(AI). All participants were completed the study without any dropouts.

Results: Neutropenia was common in both AI (88.3%) and Fluvestrant (87.2%) groups. Increase in Anemia was more marked in the Fulvestrant group (93.6%) than in AI (63.3%) with p-value <0.001), and the same for hair loss p=0.005; 46.8% and urticaria (p =0.019 , 19.1%). The mean age in each of the groups was similar (50.8 years vs 51.6 years), indicating that age did not have a significant effect on association found. As all patients had ECOG performance status of 0 to 1, performance status was not considered in the regression analysis because of lack of variability.

Conclusion: Generic Palbociclib safety profile is consistent with initial studies and historical data and it's tolerability is confirmed under-resourced settings.

Keywords: Generic Palbociclib, Metastatic breast cancer, safety profile.

1. INTRODUCTION

Breast cancer accounts for approximately one-third of all cancers in females in Iraq and an important cause of mortality [1, 2]. The most common subtype HR+/HER2− occurs in approximately 70% of all cases [3]. Now, more than 80% of women with metastatic HR+/HER2− breast cancer have received Cyclin-Dependent Kinase 4/6 (CDK4/6) inhibitors as first-line therapy in her treatment regimen, because this class of drugs has dual anti-cancer mechanisms: directly blocking the proliferation of cancer cells and increasing immunogenicity to trigger anti-tumor immunity [4]. The palbociclib schedule consists of 125 mg po qd for 21 days in a 28- day cycle followed by 7 days off. Treatment is continued as long as there is clinical benefit and the patient can tolerate toxicity [5]. In general, the CDK4/6 inhibitors are well tolerated and adverse events can be well controlled by dose adjustment and adequate supportive measures. Mild toxicities include neutropenia, diarrhea, and lethargy [6]. Additionally, CDK 4/6 inhibitors can also be related to multiple potential dermatologic toxicities, and the most commonly described dermatological adverse event is alopecia [7-9]. In response to the prohibitive cost of the original drug, Iraq implemented national generic versions. The generic formulation used in this study was manufactured by Iraqi Pharmaceutical Industry Company IPI and has established regulatory bioequivalence. This was confirmed in a formal bioequivalence study conducted at the Pharmaceutical Research Unit / Arab Pharmaceutical Industry Consulting Co. (Report No. PALB22083/Rep-00, issued April 2023). Pharmacokinetic studies are employed to confirm regulatory bio-equivalence; however clinical safety must be confirmed in the local populations[10]. The primary objective of this study is to evaluate the safety and tolerability of generic palbociclib between Iraqi women with breast cancer by assessing if the safety of generic treatment aline with data from original clinical data because of lack of local clinical data. Also to compare between regimes by comparing the frequency and severity of adverse events. Other objectives is to evaluate weather this affordable generic drug is safe and effective in patients within the Iraqi health system.

2. PATIENTS AND METHOD

2.1. Material and Methods

A prospective non-randomized comparative observational study was conducted in period (September 2024-April 2025) in the Oncology teaching hospital of Medical city complex.

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ISSN: 1929-2260 / E-ISSN: 1929-2279/26

2.2. Study Populations

A total of 175 females aged ≥18 years, with hormone-positive, Her-2 negative metastatic breast cancer (mBC), with adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 were included and completed their follow up during **the** period of study without any dropouts. Patients with bone marrow infiltration, received radiotherapy during the trial period, or symptomatic or untreated chronic illnesses were excluded. And to prevent any large baseline confounding, any patients presenting with visceral crisis or inadequate organ function because of the high disease burden were also excluded, these patients were directly converted to rescue chemotherapy at the time of data collection.

2.3. Baseline Status of Study Populations

All patients who included in this study were having normal baseline complete blood counts and adequate organ function before initiating palbociclib.

2.4. Treatment Protocol

128 females on generic Palbociclib(Palbociclib IPI) that was industrialized by Iraqi pharmaceutical Industry company, with combination to Aromatase inhibitors(P+AI), as first line endocrine treatment and the remaining 47 females received it in conjunction to Fulvestrant (P+F). Fluvestrant was used as a second line treatment for patients who presented with disease recurrence when they were on or after completing adjuvant AI treatment. A total mean age between both of these treatment groups (50.8 vs 51.6 years) respectively.All patients received national generic Palbociclib 125 mg once daily from day 1 to day 21 of a 28-day cycle with a rest of seven days. The median follow up period was about 6 cycles of treatment. New adverse events that arise from Palbociclib treatment initiation in a patient are graded according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). Laboratory tests were performed at the end of cycles off week; if cycle was deferred, samples were repeated on day 1.As no patients discontinued their treatment permanently during their course of treatment because of haematological adverse events, so clinical adjustments were needed:

Delayed doses: recurrent severe neutropenia in grade 3 and 4 needed a temporary delaying for the dose, of one week at the end of the cycle off week before repeating the laboratory tests on day 1. Reduction of the dose was not evaluated because of limited availability of alternative generic doses with Lower strength at the Time of the study.

Supportive care: Febrile neutropenia was treated with granulocyte colony stimulating factor (G-CSF). On the other hand anemia were treated with oral iron or transfusions of packed red blood cell depending on symptoms and grade of CTCAE.

2.5. Data Collection

All demographic data were Collected directly from the patients. Adverse events were collected depending on the patient's health records during their meeting with their physicians in the hospital.

2.6. Ethical Considerations

Ethics committee approval was granted by the hospital's scientific and ethical council **(**Approval No. 2347. Date September 29, 2024) and each participant signed a consent form underlining confidentiality of their data.

2.7. Statistical Analysis

Descriptive statistical analysis were used to determine the safety profile for the study population. Count of patients was expressed in absolute frequencies and percentages. Dependent variables were examined with Pearson Chi-square or Fisher's exact tests. To decrease the risk of type I errors resulting from multiple clinical comparisons, Bonferroni correction was applied to the significant level,(significant if $P<0.05$). Age was added as a covariate in the logistic regression model as an adjustment for possible confounding. The intensity of cumulative dose was not determined.

3. RESULTS

Table **1** shows the percentages and frequencies of haematological adverse events and their severity in both Palbociclib + aromatase inhibitors (P+AI) and Palbociclib+ Fluvastrant (P+F) groups. Neutropenia was one of the most common adverse effects that appeared in both groups, with sever cases account for (11.71%) in (P+AI) group and (8.51%) in (P+F) group, while anemia had a higher incidence in the (P+F) group, which was statistically significant ($p<0.001$) as shown in Table **2**. Both thrombocytopenia and febrile neutropenia were of lower incidence than other haematological adverse events.

Table 1: Hematological Adverse Events and their Severity

Adverse events	All grades		moderate		Severe	
	P+AI (128)	P+F (47)	P+AI	P+F	P+AI	P+F
Neutropenia	113 (88.28%)	41 (87.23%)	60(46.87%)	22(46.80%)	15(11.71%)	4(8.51%)
Anemia	81 (63.28%)	44(93.61%)	23(17.96%)	14(29.78%)	3(2.34%)	2(4.25%)
Thrombocytopenia	8 (6.25%)	3(6.38 %)	6(4.68%)	1(2.12%)	2(1.56%)	0

Table 2: Haematological and Non-Haematological Adverse Events Comparing Variables

Adverse events (all grades)	P+AI (128)	P+ F (47)	P. Value
Haematological adverse effects			
Neutropenia	113 (88.28%)	41 (87.23%)	0.851
Anemia	81 (63.28%)	44(93.61%)	< 0.001
Thrombocytopenia	8 (6.25%)	3(6.38 %)	0.975
Febrile neutropenia	13 (10.1%)	5 (10.6%)	0.925
Non- haematological adverse effects			
Nausea & vomiting	15 (11.71%)	2 (4%)	0.142
Diarrhea	12 (9%)	8 (17%)	0.158
Constipation	2 (1%)	1 (2%)	0.796
Urticaria	9 (7%)	9 (19.1%)	0.019
Increased weight	3 (2%)	1 (2%)	0.932
Mouth ulcer	12 (9%)	3 (6%)	0.531
Hair loss	32 (25%)	22 (46%)	0.005
Arthralgia	26 (20.31%)	10 (21%)	0.888
Fatigue	49 (38.28 %)	22 (46%)	0.311
Increased liver enzymes	2 (1%)	0 (0%)	0.384
Dyspnea	5 (3%)	1 (2%)	0.573

Table **2** shows the frequencies and percentages of both haematological and Non haematological adverse events and compares between them. In Palbociclib+AI group, the most frequent nonhematologic adverse events were fatigue (38.28%), hair loss (25%), arthralgia (20.31%).

Nausea reported in first 2 to 3 cycle and all resolved with symptomatic treatment.

In the Palbociclib+Fulvestrant group, the most frequent adverse events were fatigue (46%) and hair loss (46%).Urticaria showed a statistical significance (p=0.019) in (P+F) group compared to (P+AI) group, but in most cases it was mild and recovered spontaneously or with symptomatic treatment. On the other hand, hair loss also was statistically significant in fluvestrant group (p=0.005). All non-hematological adverse events were mild to moderate and did not affect overall quality of life of patients on treatment schedule.

Table **3**, provides Binary logistic regression, which was performed to adjust for age and resulted in higher odds of developing anemia between palbociclib + fulvestrant (P+F) and palbociclib + aromatase inhibitors (P+AI) patients (adjusted OR = 8.51, $p < 0.001$). Likewise, the P+F was linked to an increased odds of hair loss (adjusted OR = 2.64, $p = 0.005$) and urticaria (adjusted OR = 3.13, $p = 0.019$). The mean age in each of the groups was similar (50.8 years vs 51.6 years), indicating that age did not have a significant effect on association found. As all patients had ECOG performance status of 0 to 1, performance status was not considered in the regression analysis because of lack of variability.

Table 3: Adverse Events Logistic Regression Analysis Adjusted for Age

Variable (P+F vs P+AI)	Outcome	Adjusted OR	95% CI	p-value
Treatment group	Anaemia	8.51	2.5-28.5	<0.001
Treatment group	Hair loss	2.64	1.3-5.4	0.005
Treatment group	Urticaria	3.13	1.1- 8.7	0.019

4. DISCUSSION

With a mean age of 50.8 versus 51.6 years, the similarity of treatments group indicates that age will not constitute a relevant confounding factor for participation in this study, hence supporting the robustness of these observed associations between therapy regimen and adverse events. This observation mirrors previous clinical/real-world data of CDK4/6 inhibitors which showed that age does not have a major influence on safety when the functional status of the patient is preserved [6,11]. In addition to the aforementioned, all patients recruited in this study had an ECOG performance score of 0–1, reflecting the good performance capability. This ensured a fairly homogeneous study population and might explain the overall tolerability of treatment seen. Patients with good performance status exhibited manageable toxicity profiles and low discontinuation rates despite a high incidence of neutropenia in pivotal trials including PALOMA-2 and PALOMA-3 [12,13]. The results of this study exhibit that (P+F) group showed higher rates of anemia (93.61%) and hair loss (46%). Because all toxicities were presented or increased after beginning of generic palbociclib, this difference is highly caused by the patient history of treatment line. As the Fluvestrant arm consisted mainly of patients that were receiving the second line treatment after failing AI, these individuals presented with history of prior exposure of systemic chemotherapy. So this history of exposure impairs the bone marrow baseline reserves and results in increased hair follicle toxicity, which explain the higher rate of hair loss and anemia compared to endocrine arm which represents the first line of treatment.

Results of the neutropenia in our study (88.3%) are aligned with PALOMA-2 (80%) and PALOMA-3 (83%) [11, 12]. Nevertheless, the substantially greater incidence of anemia and alopecia seen in the Fulvestrant population suggests that these patients — usually candidates for second-line therapy — can exhibit less bone marrow reserves or greater cumulative toxicity [14]. In addition, generic Palbociclib did not have any novel safety signals, nor were any patients required to discontinue the drug due to hematological toxicity, which supports the implementation of this agent as an effective and affordable choice within the Iraqi healthcare system. Actual evidence is also compatible with and in favor of CDK4/6 inhibition in daily clinical practice [11]. Although the rate of neutropenia presented in the present study [88.3% in the P+AI arm group] is a class effect of CDK4/6 inhibition. In contrast to chemotherapy-induced neutropenia that results from the destruction of hematopoietic stem cells, neutropenia induced by palbociclib is the result of “quiescence”, a reversible cell cycle arrest of bone marrow precursors, this special mechanism makes it clear that when there are high rate of neutropenic events that need a delay of one week cycle and correction with G-CSF administration, no patient in this study required permanent discontinuation of therapy.

It might partly account for the fact that even though Grade 3/4 neutropenia rates were equal, none of Iraqi patients permanently withdrew a treatment as a consequence of any hematological toxicity [15,16]. In addition to cell cycle arrest, CDK4/6 inhibitors have been demonstrated to have immunomodulatory effects in the tumor microenvironment. Pre-clinical studies have shown that these agents may promote antitumor immunity through the induction of antigen presentation and T-cell activation [17]. Besides cell cycle arrest, it has been shown recently that CDK4/6 inhibitors like Palbociclib might be involved in tumor microenvironment modulating activities, where this modulatory effect strengthens anti-tumor immunity via amplified antigen presentation [18]. This enhances the therapeutic benefits by suggesting that a clinical benefit seen in patients could potentially extend beyond just cytostasis[19]. There is certainly not much agreement on this side when compared to Abemaciclib and Ribociclib. While Abemaciclib is more associated with gastrointestinal toxicity (diarrhea), myelosuppression continues to be the main hurdle for Palbociclib [20, 21]. Our report of controllable gastrointestinal symptoms (diarrhea <10%) also highlights how Palbociclib is another drug tolerability for those with baseline GI sensitivities [22]. For drug compliance in Iraq due to

socio-economic reality, generic formulations are needed. Late-stage presentations in war-affected or recovering areas constitute the “human cost” of cancer care [23]. According to the international consensus guidelines (ABC4/5), endocrine therapy remains the standard treatment, and the presence of a CDK4/6 inhibitor is vital for maintenance of adequate progression-free survival [24,25]. The skin toxicities, including urticaria (19.1% in P+F group), should be treated with caution. Because they are almost always mild to moderate, they will require an early therapeutic approach of taking antihistamines or topical steroids [26].

The skin toxicities associated with CDK4/6 inhibitors may be under-represented in important studies but remain frequent in real-world settings, such as is the case for our Baghdad trial cohort [27]. But the study was only performed in a single center, limiting the extent to which this is relevant to other groups or different healthcare settings, especially outside of Iraq or similar resource-limited settings.

Study limitations: there are many limitations need to be acknowledged in this study

1. The sample size was structurally imbalanced between the first line P+AI (128 patients) and second line P+ F (47 patients). Because this study is an observational nonrandomised study, absence of multi variable adjustments for treatment lines that were used before, baseline of hemoglobin levels and disease durations limits the ability to isolate drugs combination effects from baseline patient state.

2. Absence of reference arm, as there was no parallel comparison with the branded drug which limits the generalizability of the true safety conclusions beyond the observations of safety.

3. Selection bias: the inclusion of only ECOG 0–1 patients reduces the generalizability of findings to poorer performance type patients.

5. CONCLUSION

Safety profile of generic palbociclib was in agreement with published clinical trials yet no new safety signals were identified. Adverse events were manageable, despite a high frequency of neutropenia, with minor cycle postponements and standard supportive care, avoiding permanent treatment discontinuation. Baked by verified local bioequivalence report, these results suggest the potential in clinical settings of generic palbociclib to be tolerated in real-life, resource-challenged settings including that of Iraq. In this preliminary study we recommend that future studies to be done in larger, multicenter cohorts and inclusion of comparative groups to improve precision and generalisability.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not for profit sectors.

CONFLICT OF INTEREST

The authors declare that there are no relevant financial or non- financial competing interests to report.

AUTHORS CONTRIBUTION

Rawaa Abdulzahra Mohammed Hussein collection of data and reviewing the cited studies.

Abeer Abdulhadi Rashid writing manuscript and doing statistical analysis

Zahraa Matheel Nasir: collection of data

ACKNOWLEDGEMENT

The author like to acknowledge the support supplied by Mustansiriyah university/college of pharmacy in Baghdad. Iraq.

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Received on 21-04-2026 Accepted on 24-05-2026 Published on 09-06-2026

https://doi.org/10.30683/1929-2279.2026.15.13