

Real-World Experience of Palbociclib-Induced Adverse Events and Compliance With Complete Blood Count Monitoring in Women With Hormone Receptor–Positive/HER2-Negative Metastatic Breast Cancer

Geoffrey Alan Watson, Oana Deac, Razia Aslam, Richard O'Dwyer, Antonia Tierney, Sue Sukor, John Kennedy

Abstract

Palbociclib therapy in hormone receptor–positive metastatic breast cancer patients may result in adverse events such as neutropenia, and stringent monitoring of complete blood count is advised. The current study found good compliance with guidelines and demonstrated that dose adjustments are not associated with progressive disease. We also report a high incidence of thromboembolic events.

Background: The cyclin-dependent kinase 4/6 inhibitor palbociclib has emerged as a novel therapeutic agent in metastatic breast cancer. Neutropenia is commonly observed, and thus stringent treatment guidelines regarding complete blood count (CBC) monitoring have been developed. The aim of this study was to provide a real-world experience of the toxicities associated with palbociclib therapy and to evaluate compliance with CBC monitoring.

Patients and Methods: We performed a retrospective single-center audit of hormone receptor–positive metastatic breast cancer patients treated with palbociclib over a 6-month period in an Irish tertiary referral hospital. **Results:** A total of 64 patients were included in the analysis. Palbociclib was most commonly used in combination with letrozole ($n = 40$). A total of 28 patients (44%; 95% confidence interval, 31.2–56.2) had treatment deferrals due to neutropenia, with a median time to first deferral of 4 weeks. Fifteen patients (23%; 95% confidence interval, 15.4–37.7) required dose adjustments; however, there was no association with an increased risk of progressive disease ($P = .56$). Only 3 patients discontinued treatment as a result of poor tolerance. Adverse events were as expected; however, 7 venous thromboembolic events were reported. **Conclusion:** Compliance was good with existing CBC monitoring guidelines. We observed an 11% incidence of venous thromboembolic events, a significant increase from 2% reported in the PALOMA-3 trial. Further studies are recommended to determine if prophylactic anticoagulation may benefit these patients.

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Keywords: Cyclin-dependant kinase (CDK), Dose adjustment, Neutropenia, Thromboembolic events, Thromboembolism

Introduction

Breast cancer is one of the most common cancers to affect women and is a leading cause of cancer-related deaths worldwide. Approximately 90% of these deaths are attributed to metastatic

spread of disease.¹ In Ireland, approximately 2800 new cases of invasive breast cancer are diagnosed every year.²

Significant progress has been made in breast cancer therapeutics in recent years. Endocrine therapy is the cornerstone of treatment for hormone receptor (HR)-positive breast cancer, targeting and blocking the estrogen receptor signaling pathway. Approximately 75% of patients with metastatic breast cancers (MBC) have estrogen receptor– and progesterone receptor–positive disease.³ These receptors represent important therapeutic targets. The success of this targeted approach has been clearly demonstrated by the development of antiestrogens such as tamoxifen and the aromatase

Department of Medical Oncology, St James's Hospital, Dublin, Ireland

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Address for correspondence: Geoffrey Alan Watson, MuDr. General Medicine, Department of Medical Oncology, St James's Hospital, Dublin, Ireland
E-mail contact: Gwatson@stjames.ie

inhibitors. Unfortunately, however, the disease of most patients will acquire resistance to hormone treatment. Recent clinical research has focused on the development of novel therapeutic options to overcome this resistance, enhancing outcomes of endocrine-based therapy and delaying the need for chemotherapy, and thus ultimately optimizing outcomes for patients with metastatic disease.^{4,5}

The role of cell-cycle signaling in both breast cancer oncogenesis and antiestrogen resistance has emerged as a promising area of research. Dysregulated mechanisms governing the cell cycle are considered a hallmark of cancer and result in uncontrolled cellular proliferation.⁶ There is good evidence that the uncontrolled formation of cyclin D₁ and cyclin-dependent kinase (CDK) 4/6 complexes plays an integral role in both the initiation and progression of many cancers, including breast cancer, and may be associated with endocrine resistance.^{7,8} CDKs, a large family of serine threonine kinases, play an important role in regulating cell-cycle progression.

Palbociclib (Ibrance; Pfizer) is a small-molecule inhibitor of CDK4 and -6. In vitro studies have demonstrated palbociclib's ability to preferentially inhibit the growth of estrogen receptor-positive breast cancer cells and have also demonstrated synergy when used in combination with antiestrogens.⁹ These findings led to the design and implementation of the PALOMA trials, combining palbociclib with letrozole (PALOMA-1 and -2) and fulvestrant (PALOMA-3), and ultimately led to its approval as a novel therapeutic agent in hormone receptor-positive MBC after demonstrating significant prolongation of progression-free survival in these patients.^{8,10,11}

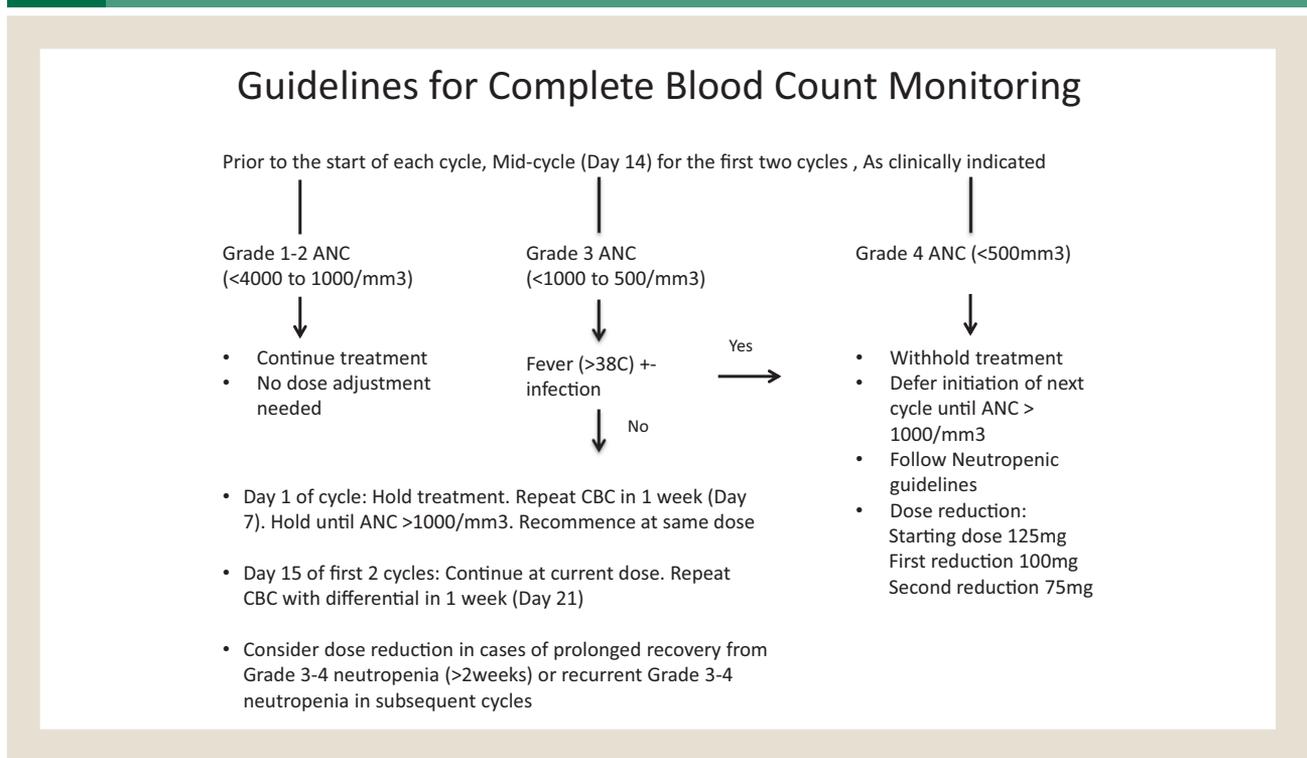
The PALOMA trials also reported a manageable safety profile, with neutropenia, often uncomplicated, the most frequently reported adverse event (AE) associated with palbociclib treatment. The neutropenia associated with CDK4/6 inhibitors is distinct from chemotherapy-induced neutropenia in that it is rapidly reversible, reflecting a cytostatic effect on neutrophil precursors in the bone marrow, rather than the apoptotic effect observed with chemotherapy.¹² Accordingly, palbociclib dosing patterns are subject to temporary discontinuation, or treatment breaks, to facilitate hematologic recovery. The incidence of febrile neutropenia is very low (0 in PALOMA-1, 0.6% in PALOMA-3), however.^{10,11} Consequently, complete blood count (CBC) monitoring guidelines are now in place to guide physicians and includes options such as treatment deferral or dose adjustment if necessary¹³ (Figure 1).

The aim of our study was to provide a real-world experience of the AEs and dosing patterns reported in HR-positive/human epidermal growth factor receptor 2 (HER2)-negative MBC in our center, as well as to evaluate compliance with established CBC monitoring guidelines.

Patients and Methods

We performed a retrospective single-center analysis of HR-positive MBC patients treated with palbociclib over a 5-month period (August–December 2017) in an Irish tertiary referral hospital (St James's Hospital, Dublin, Ireland). Patients were identified using our pharmacy database. Clinical data were collected from medical records and from laboratory and radiology reports. Pre- and postmenopausal women were included in the analysis, and

Figure 1 CBC Monitoring Guidelines and Management of Neutropenia



Abbreviation: CBC = complete blood count.
Adapted from Spring et al.¹³

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menopausal status was determined both clinically and biochemically using estradiol, luteinizing hormone, and follicle-stimulating hormone levels as an indication of menopausal status.

Palbociclib was administered at the recommended initial dose of 125 mg once daily, with food, for 21 consecutive days, followed by 7 days off treatment, constituting a total cycle of 28 days.

Laboratory assessments and CBCs were performed at baseline on day 1 of each cycle and on day 15 of the first 2 cycles. Additional tests were performed as clinically indicated according to the physician's discretion, based on AEs or planning dose adjustment. AEs were recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.¹⁴ Neutropenia was classified as grade 1 (absolute neutrophil count [ANC] < 4000/mm³ (lower limit of normal) and > 1500/mm³), grade 2 (ANC < 1500/mm³), grade 3 (ANC < 1000/mm³), or grade 4 (ANC < 500/mm³). A biochemical response to treatment was defined as a 20% reduction in cancer antigen (CA) 15-3 levels.

Clinical data were merged into a single database, and unique patient identifiers were assigned to protect patient confidentiality. The database was locked on December 8, 2017. Statistical analysis was performed by SPSS 24.0 software. The Pearson chi-square test was used to determine the statistical significance between ANC < 4000/mm³ and ANC > 4000/mm³ categories. The Mann-Whitney *U* test was used to determine significance across independent samples. The significance level was set at *P* < .05.

Results

A total of 64 patients with HR-positive MBC were included in the analysis. The median age was 62.5 years (Table 1). Fifty-one patients were postmenopausal before initiating palbociclib, and 13 patients were premenopausal. Sites of metastasis before initiating palbociclib included bone (n = 46), liver (n = 25), lung (n = 23), and brain (n = 4). Forty patients (62.5%) had multiple sites of metastasis before starting treatment. The median number of previous treatments (in the adjuvant and metastatic setting) including chemotherapy was 3, while the median number of previous endocrine therapies was 2. A total of 21 patients had received chemotherapy in the metastatic setting before commencing palbociclib. Twenty-six patients (40%) commenced palbociclib as first-line treatment, while 10 patients (16%) commenced palbociclib as first-line treatment for de novo metastatic disease.

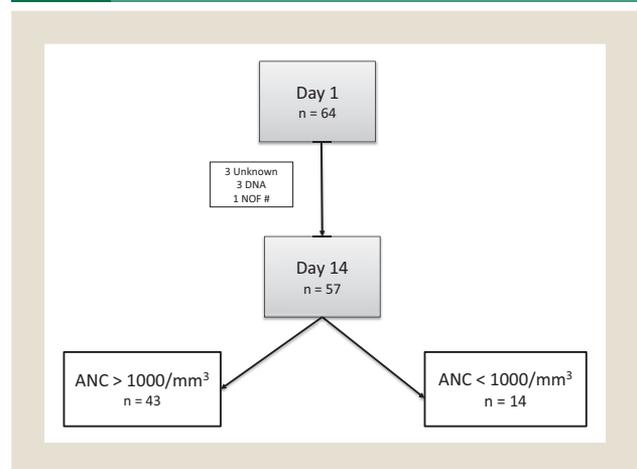
Palbociclib was most commonly used in combination with letrozole (n = 40). Faslodex (n = 20), tamoxifen (n = 2), and exemestane (n = 2) were also used in combination with palbociclib. The median follow-up was 20 weeks. The median number of cycles completed was 5 (range, 1-9), and the median number of weeks on treatment was 20 (range, 1-36).

CBC Monitoring

All 64 patients had a routine CBC check on the day of commencing palbociclib (day 1) (Figure 2). Of these, 89% (57/64) returned for a blood check at day 14. Of the 7 patients who did not

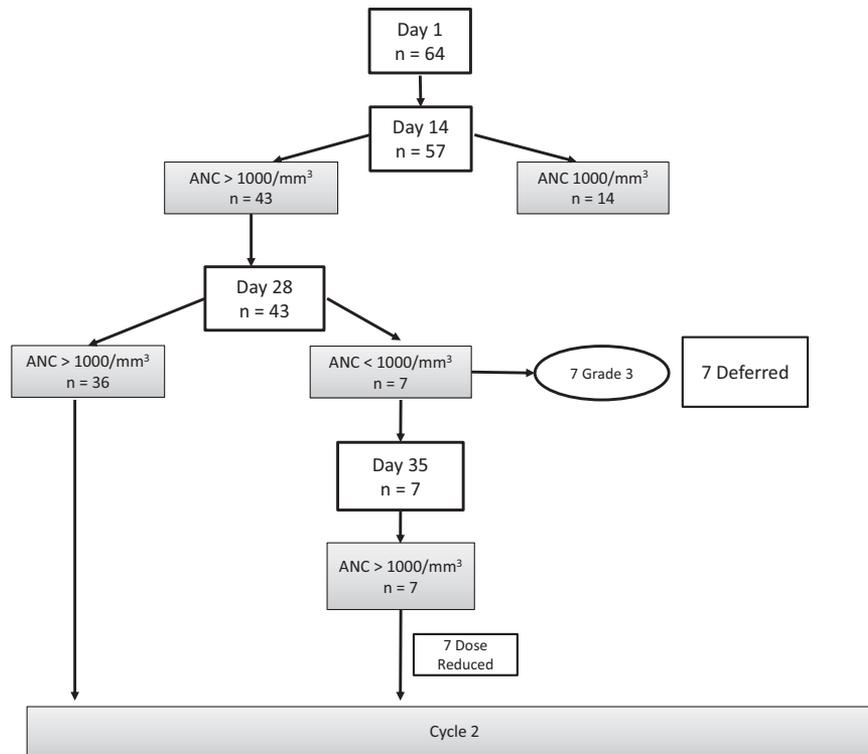
Table 1 Demographics in 64 Patients With Hormone Receptor –Positive Metastatic Breast Cancer	
Characteristic	N
Age, y	
<50	27
50-65	20
>65	17
Menopausal Status	
Premenopausal	13
Postmenopausal	51
Disease Stage	
Recurrent	54
De novo	10
Site of Metastatic Disease	
Bone	46
Liver	25
Lung	23
Brain	4
Multiple sites	40
Previous Treatments (Adjuvant and Metastatic Settings)	
0	10
1-2	21
>3	33
No. of patients receiving prior chemotherapy in metastatic setting	21
Treatment Setting (Palbociclib)	
First line	26
More than first line	38
Combination Treatment	
Letrozole	40
Faslodex	20
Exemestane	2
Tamoxifen	2

Figure 2 CBC Monitoring on Days 1 to 14. Fifty-seven (89%) of 64 Patients Returned for Blood Check on Day 14. Forty-three Patients (75%) had ANC > 1 on Day 14, and 14 (25%) of 57 Patients were Neutropenic on Day 14



Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count.

Figure 3 CBC Monitoring in Nonneutropenic Patients on Day 14. Fifty-seven (89%) of 64 Patients Returned for Blood Check on Day 14. Forty-three Patients (75%) had ANC > 1 on Day 14 and Proceeded to Blood Check on Day 28. Of these, 36 had ANC > 1 and then Proceeded to Cycle 2



Abbreviation: ANC = absolute neutrophil count.

have CBC check on day 14, 1 patient experienced a fracture of the femur neck, while 6 patients did not attend.

A total of 43 patients (67%; 95% confidence interval [CI], 55.4-79.0) had ANC > 1000/mm³ at day 14 and proceeded to a blood check at day 28 (Figure 3). Of these patients, 36 had ANC > 1000/mm³ and then proceeded to cycle 2. At day 28, 7 patients had ANC < 1000/mm³, and all 7 patients were deferred with grade 3 neutropenia, with repeat blood tests on day 35. The ANC for all these 7 patients was > 1000/mm³ on day 35, and they proceeded to cycle 2. All 7 patients had their dose of palbociclib adjusted to dose level -1 (100 mg).

Fourteen (25%) of the 57 patients had neutropenia on day 14 (Figure 4). Of these, 13 patients had grade 3 neutropenia, and 1 patient had grade 4 neutropenia. Eleven of these patients (79%) had repeat blood samples taken on day 21. The remaining 3 did not attend for a day 21 blood test. Of the 11 patients with day 21 blood samples, 9 patients had persistent neutropenia (5 grade 3, and 4 grade 4). All 14 of the patients who had neutropenia at day 14 had blood samples taken again on day 28. Six patients proceeded to cycle 2 with ANC > 1000/mm³. The remaining 8 patients (57%) had persistent neutropenia. All 8 patients were deferred, and all 8 had repeat blood samples taken at day 35. ANCs were > 1000/mm³ in 5 patients; however, 3 patients remained neutropenic at day 35, and had treatment deferred until their neutrophil counts recovered

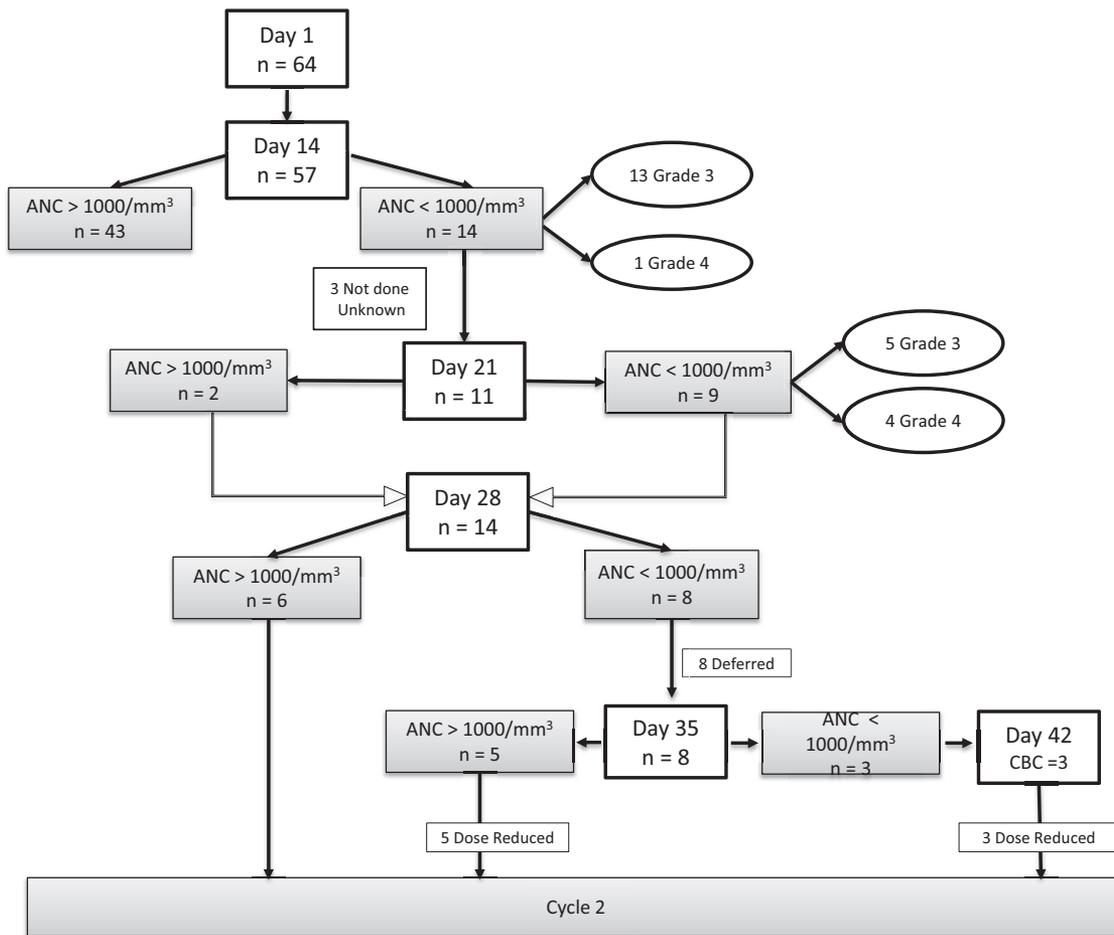
(ANC > 1000/mm³). All 8 patients were dose adjusted to dose level -1 (100 mg) before commencing cycle 2.

Response

Eleven patients (17%; 95% CI, 8.1-27.9) had a radiologic response after 3 months, while 14 patients (21% CI 10.2-30.4) had stable disease at their first staging computed tomographic scan (Figure 5). Twenty-one patients (33%; 95% CI, 21-44.6) had evidence of radiologic progression. Six patients experienced clinically or biochemically progressive disease before their restaging scan, while 12 patients were still awaiting their first restaging scan at the time of database lock. Fifteen patients showed a biochemical response in terms of CA 15-3 levels at the time of database lock. A total of 29 patients had a stable CA 15-3 at the time of database lock. The disease of 13 patients demonstrated rising CA 15-3 levels during treatment. In 3 patients the CA 15-3 level was unknown, and 4 patients had experienced clinical progression or had their treatment discontinued before the measurement of the first CA 15-3.

The main cause for discontinuing treatment was progression of disease (n = 30) (Figure 6). Median time to progression was 12 weeks. Three patients discontinued as a result of poor tolerance, 2 patients died of disease, and 1 patient discontinued treatment because of a fracture of the femur neck. One patient temporarily discontinued treatment after experiencing disease progression in the

Figure 4 Neutropenia on Day 14. Fourteen (25%) of 57 Patients were Neutropenic on Day 14. Thirteen Patients had Grade 3 Neutropenia, and 1 Patient had Grade 4 Neutropenia



brain only, with stable systemic disease. A total of 28 patients were still receiving treatment with palbociclib at the time of database lock, and 89% (57/64) patients were still alive at the time of database lock.

Adverse Events

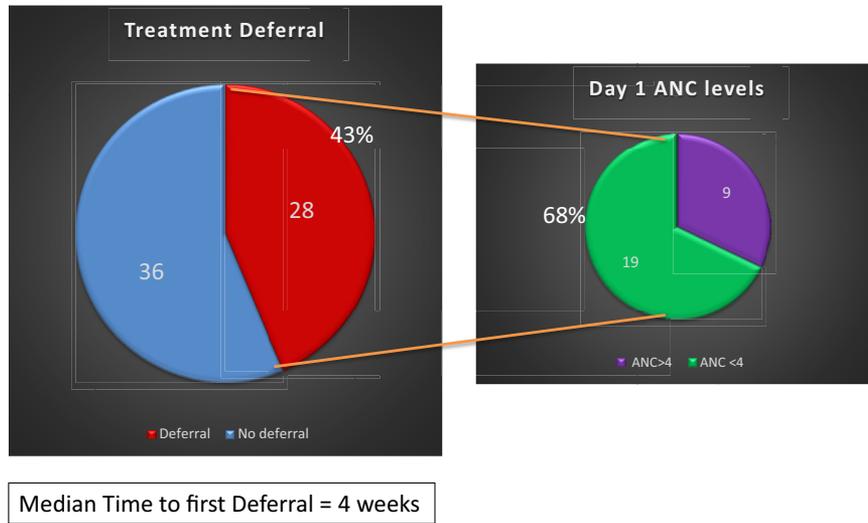
During therapy with palbociclib, 12 patients had one hospital admission, and one patient was admitted twice. The most common AE was neutropenia, documented in 61 of 64 patients during the course of treatment. Only one patient had normal ANC levels throughout treatment. Two patients experienced clinical disease progression or discontinued treatment before their first blood check.

A total of 28 patients (44%; 95% CI, 31.2-56.2) had treatment deferrals because of neutropenia, with a median time to first deferral of 4 weeks (Figure 7). Nineteen of these deferred patients (68%) had ANC < 4000/mm³ before initiating palbociclib. Ten of these patients (53%) had bone metastases; however, the presence of bone metastases was not associated with neutropenia (P = .42). Only one patient developed febrile neutropenia. In total, 17 patients (26%; 95% CI, 15.4-37.7) required dose adjustments, with 16 patients dose

adjusted because of neutropenia (Figure 7). One patient had the dose adjusted because of grade 3 fatigue. Median time to first dose reduction was 6 weeks. Of the 17 patients who had their dose adjusted to 100 mg (dose level -1), 4 patients required a further dose adjustment to 75 mg (dose level -2). Three patients discontinued treatment because of poor tolerance (all 3 patients with grade 3 nausea and fatigue) (Figure 8). Patients with ANC < 4000/mm³ at day 0 were more likely to be neutropenic on day 14 (P = .0001) and were more likely to require dose adjustments (P = .001). However, ANC < 4000/mm³ on day 1 of treatment was not associated with earlier treatment cessation (P = .39). Patients with dose reductions did not have an increased likelihood of disease progression (P = .56).

Other AEs reported included fatigue (n = 28), gastrointestinal complaints (n = 17), infection (n = 16), thrombocytopenia (grade 3 [$< 50,000/\text{mm}^3$ to $> 25,000/\text{mm}^3$], n = 7), anemia (grade 2 [hemoglobin < 10.0 g/dL to > 8.0 g/dL], n = 7), alopecia (n = 3), deranged liver function tests (n = 3), and decreased appetite (n = 2) (Figure 9). Seven venous thromboembolic events were recorded (6 grade 2, 1 grade 3), with one patient experiencing a saddle pulmonary embolus.

Figure 5 Response After 3 Months. Eleven Patients (17%) had Radiological Response After 3 Months, and 14 Patients (22%) had Stable Disease on their First Restaging Computed Tomographic Scan. Twenty-one Patients (33%) had Radiologic Evidence of Progression. Six Patients had Clinical or Biochemical Evidence of Disease Progression Before their Restaging Scan, and 12 Patients Still Awaited that Scan



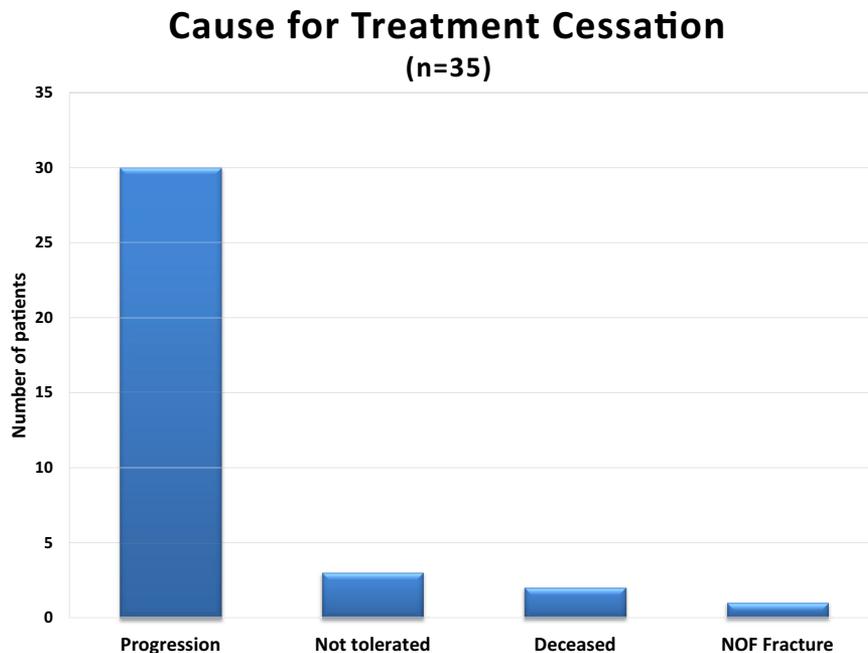
Discussion

MBC is the second most common cause of death from cancer in women, with a median overall survival of only 2 to 3 years from diagnosis and a 26% 5-year survival rate.^{15,16} Hormone therapy has been the mainstay of therapy for patients diagnosed with HR-

positive MBC. The CDK4/6 inhibitor palbociclib has recently emerged as a novel therapeutic option for these patients, and the PALOMA trials have reported a favorable toxicity profile.^{8,10,11}

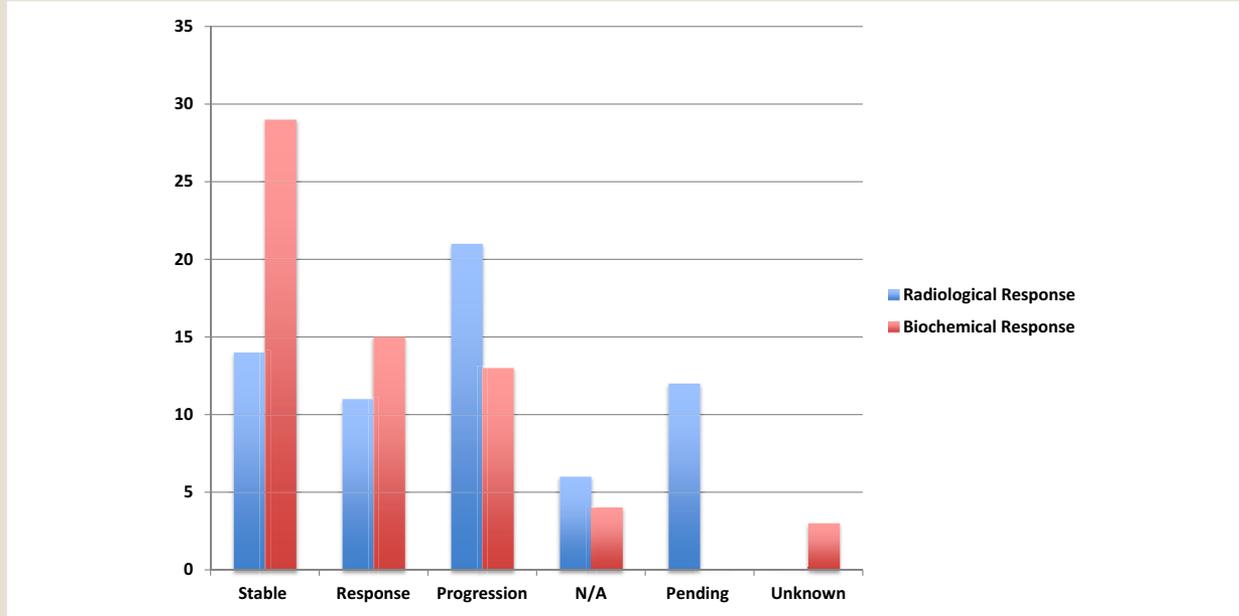
The current study reports good tolerance to palbociclib. A variety of AEs have been reported with palbociclib; however, the majority

Figure 6 Reason for Stopping Treatment. Main Cause for Stopping Treatment was Progression of Disease (n = 30). Median Time to Progression was 12 Weeks. Three Patients Discontinued Treatment as a Result of Poor Tolerance



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Figure 7 Treatment Deferrals Due to Neutropenia. Twenty-eight Patients (44%) had Treatment Deferrals Due to Neutropenia, with Median Time to First Deferral of 4 Weeks. Of these Patients, 19 (68%) had Low ANC Count of < 4 Before Initiating Treatment with Palbociclib



Abbreviation: ANC = absolute neutrophil count.

are low grade (grade 1/2). The most common AE associated with palbociclib and other CDK4/6 inhibitors is neutropenia (PALOMA-1 all grade 75% and grade 3/4 54%; PALOMA-3 all grade 81% and grade 3/4 65%).^{8,10,11} This finding was also reflected in

the current study, with 61 patients (95%) experiencing neutropenia during the course of therapy and 44% (n = 28) experiencing treatment deferrals due to neutropenia. There was only a single documented case of febrile neutropenia in the our study, which

Figure 8 Dose Adjustments. Seventeen Patients (26%) Required Dose Adjustments, with 16 Patients Receiving Dose Adjustments Due to Neutropenia and 1 Patient Due to Grade 3 Fatigue. Median Time to First Dose Adjustment was 4 Weeks. Of 17 Patients Dose Adjusted to 100 mg (Dose Level -1), 4 Patients Required Further Dose Adjustment to 75 mg (Dose Level -2). Three Patients Discontinued Treatment Because of Tolerance; All 3 Patients had Grade 3 Nausea and Fatigue

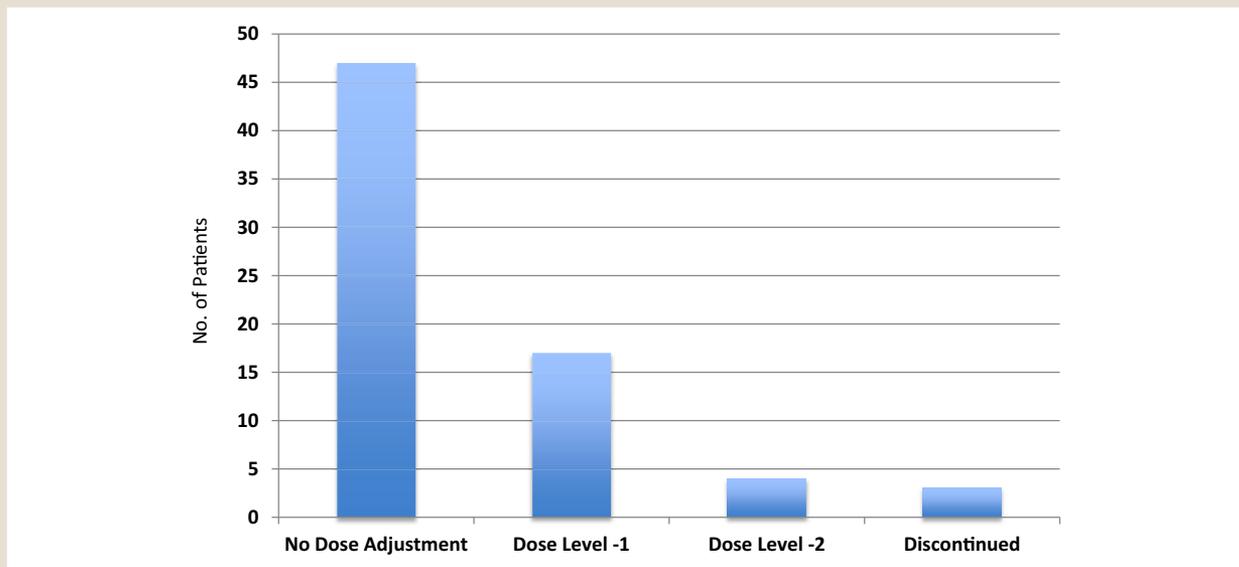
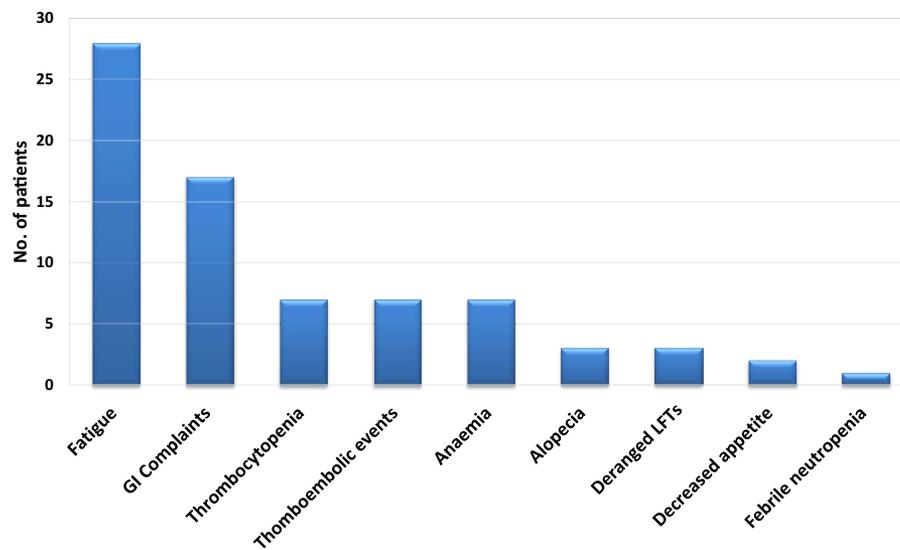


Figure 9 AEs Reported While Receiving Palbociclib Therapy. Patients Reported Fatigue (n = 28), Gastrointestinal Complaints (n = 17), Infection (n = 16), Thrombocytopenia (Grade 3, <50,000–25,000/mm³) (n = 7), Anemia (Grade 2, Hemoglobin < 10.0–8.0 g/dL) (n = 7), Alopecia (n = 3), Deranged Liver Function Tests (n = 3), and Decreased Appetite (n = 2). Seven TEs were Recorded, with 1 Patient Experiencing Saddle Pulmonary Embolus (6 Grade 2 AEs, 1 Grade 3 AE)



Abbreviations: AE = adverse event; TE = thromboembolic event.

required hospital admission. However, early neutropenic events were not associated with earlier treatment cessation ($P = .39$).

The current study also demonstrated good compliance with published CBC monitoring guidelines. A total of 89% of patients had a repeat blood check on day 14 (6 patients did not attend, and 1 experienced a fracture of the femur neck). Those with ANC > 1000/mm³ correctly proceeded to cycle 2. Those who were neutropenic were correctly deferred with repeat blood samples on day 21 and received dose adjustments in cases of prolonged ANC recovery. A similar pattern was also observed for cycle 2. In total, 17 patients (26%; 95% CI, 15.4-37.7) required dose adjustments; this finding is similar to that reported in other real-world analyses.^{17,18} Of interest, the patients who were neutropenic at day 1 were more likely to be neutropenic at day 14, and they were also more likely to have had their dose reduced. Thus, extra vigilance and education are required for these patients. Importantly, and reassuringly for the patients, dose reductions were not associated with increased likelihood of progression of disease ($P = .56$), as reflected in the PALOMA trials.^{10,11}

The other common toxicity seen with palbociclib is fatigue (PALOMA-1 41%, PALOMA-2 37.4%, PALOMA-3 39%), which is often mild.^{8,10,11,19} In the current study, 28 patients (44%; 95% CI, 31.2-56.2) experienced fatigue during the course of treatment. Gastrointestinal complaints such as nausea (PALOMA-1 25%, PALOMA-2 35%, current study 26%), vomiting, reduced appetite, and diarrhea have also been reported.^{8,10} Alopecia has also been observed in a small number of patients, with grade 1 alopecia observed in 32.9% of patients in the palbociclib group compared to 16% in the letrozole alone group in the PALOMA-2 trial.⁸ Three

patients (5%) reported alopecia in the current study. Overall, palbociclib seems to be very well tolerated, with only 3 patients (5%) discontinuing therapy as a result of AEs (3 patients with grade 3 nausea, 3 patients with grade 3 fatigue), and again, this is similar to the 7% discontinuation rate reported by Eziokwu et al.¹⁸

Venous thromboembolic events have occasionally been reported with palbociclib. In the PALOMA-1 trial, 2 patients (0.6%) in the palbociclib–letrozole arm had a nonserious event, and 4 patients (1.2%) had a serious event (3 pulmonary emboli and 1 deep-vein thrombosis).¹⁰ In the PALOMA-2 trial, pulmonary embolism occurred in 0.9% of the patients in the palbociclib–letrozole group and in 1.4% in the placebo–letrozole group.⁸ PALOMA-3 reported a 2% rate of thromboembolic events.¹¹ The current study reported a much higher incidence rate of thromboembolic events at 11%; however, it is difficult to ascertain whether these events were palbociclib related or disease related. The largest meta-analysis investigating the incidence of thromboembolic events in MBC treated with CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) involved 2671 patients and reported an incidence of 1.46% (24 patients) of thromboembolic events in the CDK4/6 group versus 0.39% in the control group, suggesting that the CDK4/6 inhibitors may contribute to the higher incidence of these events.²⁰ The higher incidence in this study may reflect more advanced disease, as a large proportion of our patients (62.5%; 95% CI, 50-75) had multiple sites of metastases before commencing palbociclib therapy, and had also been heavily treated in the past, with a median of 3 previous treatments.

The limitations of this study deserve mention. This was a retrospective study performed at a single tertiary-care site, and the

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sample size was small (n = 64). The lack of association between dose reduction and progression of disease, for example, while previously demonstrated in clinical trials, may be affected by this sample size. Nevertheless, other observations such as neutropenic events, dose adjustments, and treatment discontinuation are similar to those reported in other large real-world analyses.^{17,18}

Conclusion

There has been significant progress made in breast cancer therapeutics, and endocrine therapy remains the mainstay for hormone-positive MBC. Unfortunately, options are limited for those whose disease becomes resistant to hormone blockade. The development of novel therapeutic agents such as the CDK4/6 inhibitor palbociclib is a significant addition to the treatment armamentarium for these malignancies. To our knowledge, this is one of the largest real-world analyses of the dosing patterns, CBC monitoring, and AEs during palbociclib therapy. The current demonstrated that patients have good tolerance to palbociclib, with uncomplicated neutropenia the most common AE. Thus, stringent CBC monitoring is important, and this was again reflected in our study. If dose adjustments due to neutropenia are warranted, this was not associated with an increased likelihood of disease progression.

Of interest was the incidence of thromboembolic events in this study, which was significantly higher than that reported in previous clinical trials; clinical suspicion and awareness are thus paramount, and further studies are recommended to determine if prophylactic anticoagulation may benefit these patients. Additional research is needed to better understand the toxicity profile and to develop management strategies to minimize drug interruptions and optimize therapeutic efficacy in these patients.

Clinical Practice Points

- Our study demonstrated good compliance with existing CBC monitoring guidelines.
- Neutropenic events are often uncomplicated.
- Dose adjustments are not associated with an increased likelihood of disease progression.
- We report an 11% incidence rate of thromboembolic events, a significant increase from that reported in previous trials.
- Further studies are recommended to determine if prophylactic anticoagulation may be of benefit.

Disclosure

The authors have stated that they have no conflict of interest.

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