Original Study

European Journal of ONCOLOGY PHARMACY

OPEN

Recurrence rate in patients with stage IV breast cancer: a retrospective cohort study

Leanda Grobler, BCMP[a,b], Ané Orchard, PHD[a], Shun D. Moodley, MMBch, FCP (SA)[b], Ion Pypers, MSc[a], Razeeya Khan, MSc[a,*]

Abstract

Introduction: Metastatic breast cancer (mBC) remains incurable, with a median overall survival (OS) of approximately 3 years and a 5-year survival rate of approximately 25%, irrespective of the economic classification of the country where treatment is received. Cyclin-dependent kinase (CDK) inhibitors increase overall survival in both first and second-line settings in the treatment of hormone receptor–positive, human epidermal growth factor receptor 2–negative mBC. This retrospective cohort study investigated the progression-free survival in women with mBC receiving combination therapy with abemaciclib (CDK4/CDK6 inhibitor) and letrozole or fulvestrant as opposed to abemaciclib only.

Methods: The study included all eligible women with stage IV breast cancer treated with abemaciclib at a private oncology facility in Johannesburg over the study period. Data were collected from medical records from April 1, 2019 to March 31, 2021. Analyses were conducted to assess the overall survival rate, progression-free survival probability, and safety of abemaciclib in women with stage IV breast cancer.

Results: Thirty-two patients were eligible for inclusion in this study. The progression-free survival probability was 60% after a period of 17 months, irrespective of treatment options. After 17 months, the OS of women on a combination of abemaciclib and letrozole was 80%, on a combination of abemaciclib and fulvestrant was 80%, and on abemaciclib monotherapy was 70%. The most noted adverse effects were diarrhea (92.0%), neutropenia (92.0%), fatigue (48.0%), and hepatotoxicity (16.0%).

Discussion: Abemaciclib with endocrine therapy or an aromatase inhibitor provided an improvement in the OS compared with abemaciclib monotherapy. These findings are representative of the use of abemaciclib in a local population and are similar to those of larger studies conducted internationally.

Keywords: abemaciclib, breast cancer, progression-free survival

Introduction

Cancer remains one of the leading causes of death and a barrier to increasing life expectancy worldwide.[1] The burden of cancer incidence and mortality reflects population growth and changes in socioeconomic development.[2] The disease landscape in Africa is also undergoing significant changes, with rising morbidity and mortality due to noninfectious diseases such as cancer.[3] Epidemiological studies from a regional public sector hospital in South Africa indicated that, irrespective of the geographical status, most patients with breast cancer consulted late in both rural and periurban areas of developing countries.[4] Since the 1980s, various treatment options have been explored in an attempt to improve survival in patients with advanced breast cancer.[5]

International clinical guidelines recommend endocrine therapy (ET) as the first line of therapy for human epidermal growth factor receptor 2 (HER2)-negative, hormone receptor (HR)-positive, advanced breast cancer. However, approximately 50% of HR-positive patients develop resistance to ET within their lifetime, ultimately leading to disease recurrence and limited clinical benefit of this therapy.[6] Preclinical models suggest that HR-positive breast cancer cells display biological features that are conducive to the use of targeted therapy with cyclin-dependent kinase (CDK) 4/6 inhibitors.[6] There are currently two CDK4/6 inhibitors registered for use in South Africa: ribociclib and abemaciclib.

Emerging therapies require the skills of a multidisciplinary team (MDT) to ensure optimum patient care.[7] As the treatment landscape changes in the South African environment, it is important to reflect on the use of these medicines in local cohorts of patients to understand and enhance the contribution of professionals in the MDT.[8] For pharmacists, this includes management of medicine safety and patient education.[9]

The authors declare no conflicts of interest.

[a] *Division of Clinical Pharmacy, Department of Pharmacy and Pharmacology, School of Therapeutic Sciences, University of the Witwatersrand, Johannesburg, South Africa,* [b] *Unit of oncology, Wits Donald Gordon Medical Centre, Johannesburg, South Africa.*

** Corresponding author. Address: Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of Witwatersrand, Medical School, 7 York Road, Parktown, Johannesburg, 2193, South Africa. E-mail address: razeeya.khan@wits.ac.za (Razeeya Khan).*

The European Journal of Oncology Pharmacy (2023) 6:2(e45)

Received: 3 April 2022 / Accepted: 29 June 2023

http://dx.doi.org/10.1097/OP9.0000000000000045

This study reports on the progression-free survival (PFS) in South African women with metastatic breast cancer (mBC) receiving monotherapy with abemaciclib, combination therapy with abemaciclib and letrozole, and combination therapy with abemaciclib and fulvestrant. Analyses were conducted to assess the overall survival (OS) rate, PFS probability, and safety of abemaciclib in a local cohort of patients and to compare the findings with those in other studies.

Method

Design and participants

Ethical approval for this study (Ethical Committee clearance certificate number: M220113) was provided by the Human Research Ethics Committee of the University of Witwatersrand, Johannesburg, South Africa, on April 22, 2022. A retrospective cohort study was conducted in a private oncology facility in Johannesburg. Data were collected on thirty-two South African women with stage IV breast cancer who were enrolled in a compassionate use program with abemaciclib from April 1, 2019 to March 31, 2021. All patients had HER2-negative and HR-positive stage IV breast cancer with at least 4 or more lines of chemotherapy and ET in an early and metastatic setting. Records of patients with adequate Eastern Cooperative Oncology performance status 1; adequate renal, hepatic, and myeloid reserve; as well as normal QT corrected for heart rate interval on electrocardiogram were included.

Both premenopausal/perimenopausal and postmenopausal women were considered for participation. Women in premenopause/perimenopause received 10.8 mg of goserelin for at least 1 month before initiation of abemaciclib and continued to take goserelin every 3 months. Within this group of patients, those on monotherapy each received 200 mg of abemaciclib twice daily and those on combination therapy each received 150 mg of abemaciclib twice daily.

Each patient attended a follow-up consultation after 1 month of treatment and continued follow-up consultations on a 3-month basis. Abemaciclib use was discontinued in patients who presented with disease progression in line with the treatment protocol. Clinical retrospective data were retrieved from medical records including clinical features and radiological imaging. Informed consent for this retrospective analysis was obtained from surviving participants.

Statistical analysis

The Kaplan-Meier method was used to estimate the median PFS and median OS of all participants. Categorical data are prescribed as percentages. All statistical analyses were conducted using the STATISTICA Version 13.1 program (University of Witwatersrand, Johannesburg, 2022).

Results

Baseline characteristics

The first patient was enrolled 5 months after initiation of the compassionate use program. The data are representative of all patients enrolled over the remaining 17-month period. Of the 32 patients selected (Figure 1), five patients did not take abemaciclib because of disease progression and two patients absconded. Patients are categorized in three subgroups: (1) those on abemaciclib alone, (2) those on abemaciclib in combination with letrozole (2.5 mg) daily, and (3) those on abemaciclib in combination with fulvestrant (250 mg) once per month.

Demographic and clinical features

The median age of all patients was 52.0 (46.0–60.5) years (Table 1). Of the 25 patients on abemaciclib, 10 patients were selected at random for the use of monotherapy and 70% of these patients were postmenopausal. Five patients were selected at random for the use of abemaciclib and letrozole as combination therapy, and 60% of these patients were postmenopausal. Ten patients were selected at random for the use of abemaciclib and fulvestrant as combination therapy, and 70% of these patients were postmenopausal.

Eight of the patients were premenopausal/perimenopausal and had been treated with goserelin before initiation of abemaciclib and continued to take goserelin throughout the study. Among these women, 32.0% had lung and liver metastases; 32.0% had bone metastases; 16.0% had lung and bone metastases; 16.0%

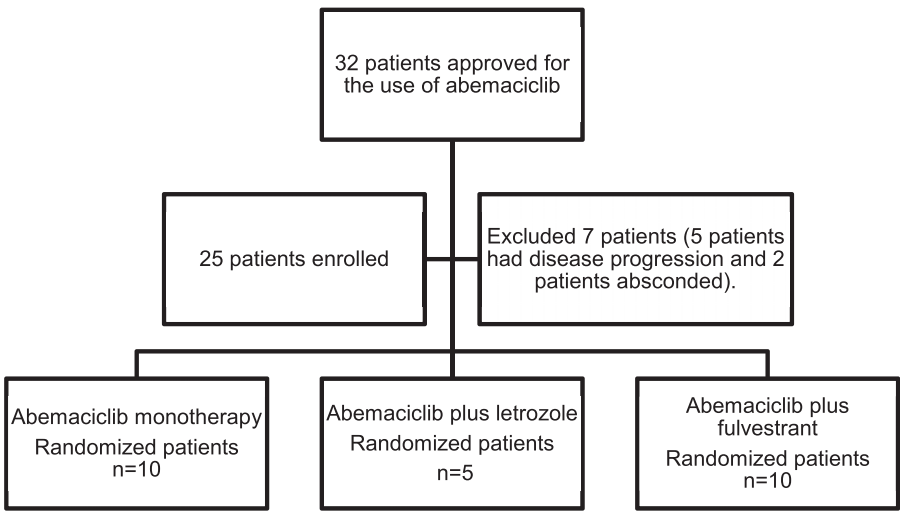

Figure 1. Subgroups of patients enrolled in the compassionate program

Table 1

Demographic and clinical features of patients with stage IV breast cancer on abemaciclib.

Characteristic	Patients (N=25)
Median age (interquartile range), years	52.0 (46.0–60.5)
Ethnic groups (%)	
White ethnicity	10 (40.0)
Black ethnicity	7 (28.0)
Colored ethnicity	4 (16.0)
Indian ethnicity	4 (16.0)
Number of patients on goserelin	
Premenopausal/perimenopausal	8
Postmenopausal (%)	
Monotherapy	7 (70.0)
Letrozole	3 (60.0)
Fulvestrant	7 (70.0)
Site of metastases (%)	
Lung and liver	8 (32.0)
Bone metastases	8 (32.0)
Lung and bone metastases	4 (16.0)
Bone and liver metastases	4 (16.0)
Lung, liver, and bone metastases	2 (8.0)
Bone and mediastinal involvement	1 (4.0)

had bone and liver metastases; 8.0% had lung, liver, and bone metastases; and 4.0% had bone and mediastinal involvement.

Adverse drug reactions were reported according to the Common Terminology Criteria for Adverse Events Version 5.0 grading scale. Severe (≥ Grade 3) diarrhea, hepatotoxicity, and neutropenia were observed in patients receiving abemaciclib (Table 2). One patient discontinued treatment because of severe diarrhea, and four patients died from the disease during the study.

Patients with diarrhea were managed with loperamide as needed and discontinuation of abemaciclib for a period of 3 days, followed by reinitiation of abemaciclib. Patients who presented with a neutrophil count of $<2.00 \times 10$ g/L were managed with discontinuation of abemaciclib and daily administration of pegfilgrastim, followed by reinitiation of abemaciclib after 7 days.

Clinical outcomes

A survival analysis is described in Figure 2. Findings from the remaining sample of 25 patients yielded a PFS of all patients at 60% after 17 months. The median probability of recurrence of all patients on abemaciclib during the 17 months was 24%. The median OS of patients on abemaciclib was 70% after 17 months.

Table 2

Severe adverse effects in patients undergoing treatment with abemaciclib (N=25).

Adverse effect	All grades (%)	< Grade 3 (%)	≥ Grade 3 (%)
Gastrointestinal disorders			
Diarrhea	92.0	60.0	32.0
Vomiting	4.0	4.0	0
Abdominal pain	4.0	4.0	0
Hepatotoxicity	16.0	0	16.0
Upper respiratory disorders			
Sinusitis	4.0	4.0	0
General disorders			
Fatigue	48.0	48.0	0
Blood and lymphatic disorders			
Neutropenia	92.0	80.0	12.0

The median OS of patients on a combination of abemaciclib and letrozole was 80% after 17 months and that of patients on a combination of abemaciclib and fulvestrant was 80% after 17 months.

Discussion

In this study, patients on abemaciclib only had a 10% lower chance of survival after 17 months than patients who had received abemaciclib in combination with ET agents specifically, letrozole and fulvestrant. Patients on ET without abemaciclib were not included in this study. As a result, the OS of patients on letrozole or fulvestrant without abemaciclib is not available. The sample size of women enrolled in the compassionate use program is small; however, the findings in this South African cohort coincide with those of international studies. The risk of disease recurrence remains below the 50th percentile after a period of 17 months. Caution should be exercised when comparing the median PFS with international studies because a multivariate analysis could not be performed.

Regarding toxicity profile, diarrhea and neutropenia were managed with minimal hospitalizations. Although four patient deaths were documented in patients with existing liver metastases, the cause of death could not be confirmed as liver failure due to abemaciclib use. It would be beneficial to investigate the number of patients with liver metastases requiring dose reductions of abemaciclib. In larger international studies, no known cases of clinically apparent liver injury attributed to abemaciclib have been reported.[10] Because abemaciclib is a substrate for cytochrome P450 3A4 (CYP 3A4), it is susceptible to drug-drug interactions with agents that inhibit or induce this specific hepatic microsomal activity.[10]

Critical review of medical records would be required to identify whether any of the four patients had any preexisting comorbidities for which they were taking treatment. There are minimal published articles that discuss abemaciclib toxicity in the South African context. The most reliable guideline available is that of the European Medicines Agency, which recommends that patients with (Child-Pugh C) hepatic impairment should decrease the dosing frequency of abemaciclib to once daily.[11] Alanine aminotransferase and aspartate aminotransferase should be monitored before the start of abemaciclib therapy, at every 2 weeks for the first 2 months, and monthly for the next 2 months.[11] The use of abemaciclib should be discontinued if the elevation in aspartate aminotransferase and/or alanine aminotransferase is >3 x upper limit of normal (ULN) with a total bilirubin of >2 x ULN, in the absence of cholestasis or in the case of Grade 4 (>20.0 x ULN) hepatotoxicity.[11] According to the European Society of Medical Oncology guidelines, it is important for the physician to recognize the difference between visceral disease and a visceral crisis. In the presence of a visceral crisis, the presence of metastases is not as important as the consideration of organ compromise, which should guide clinical management and decision making.[12]

HER2-negative, HR-positive breast cancer incidences among South African ethnic groups are widely under-reported. In this study, most of the patients were of White ethnicity (Table 1); however, it needs to be considered that this study was conducted in a private oncology facility in an urban area. To assess a true reflection of ethnicity on the CDK4/6 inhibitor therapeutic potential, a meta-analysis conducted on a larger population of South African women would be beneficial. Cost of treatment is a major barrier to the inclusion of abemaciclib as a treatment option within the breast cancer policy framework in the public

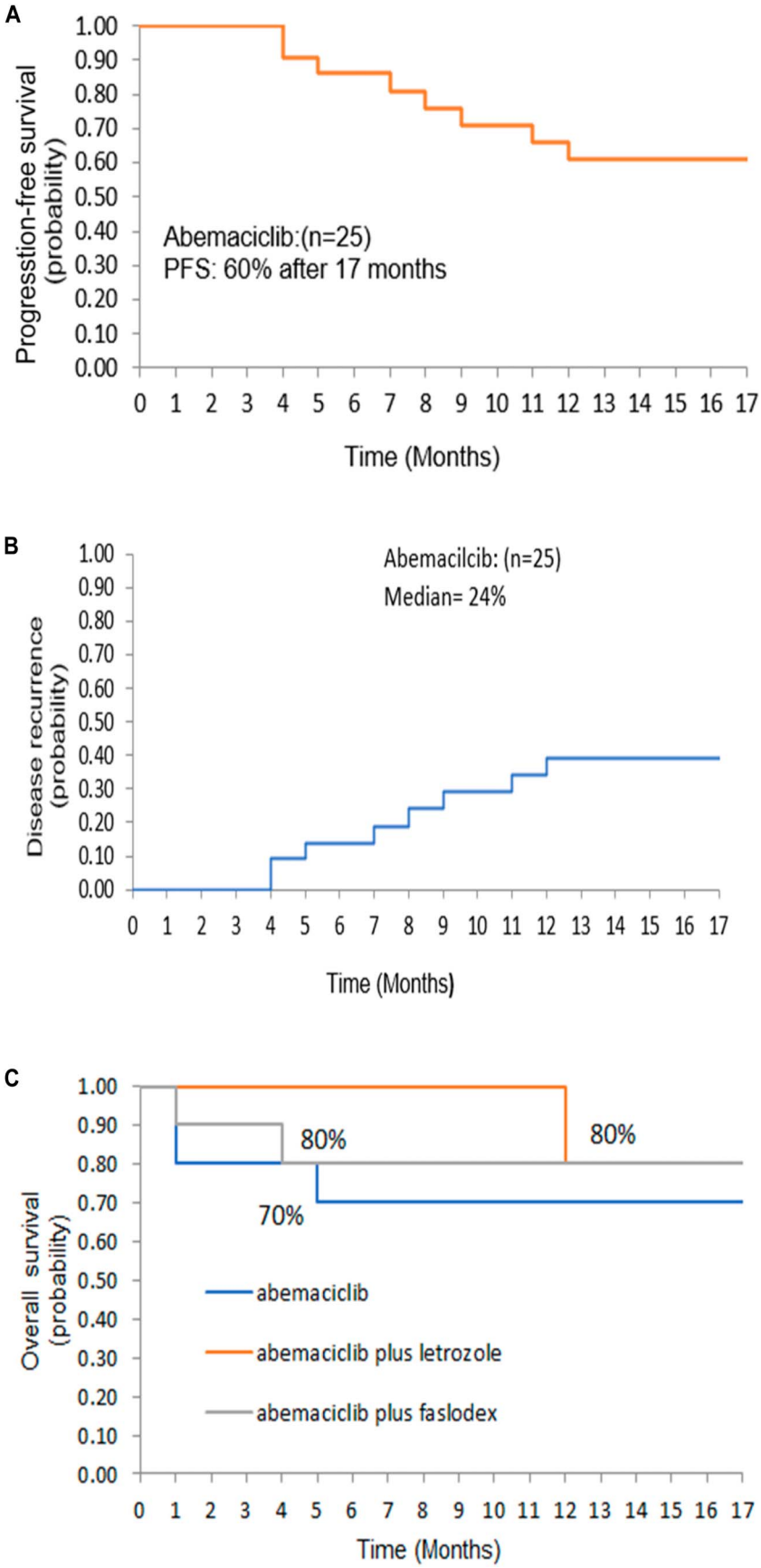

Figure 2. Survival analysis captured as Kaplan-Meier curves. (A) Kaplan-Meier plot of PFS for all patients on abemaciclib. (B) Kaplan-Meier plot of median probability of disease recurrence for all patients on abemaciclib. (C) Kaplan-Meier plot of OS for patients on abemaciclib versus abemaciclib plus letrozole versus abemaciclib plus fulvestrant.

sector in South Africa.[13] The scarcity of affordability data is one of the major barriers in the development of an effective pricing policy in low-middle income countries.[14]

In conclusion, this analysis indicates that patients who were eligible for the compassionate use program received beneficial treatment with minimal risk while on monotherapy or combination therapy with abemaciclib for mBC. The findings of this study provide focus for the management of patients receiving abemaciclib by the MDT. Education and early screening within rural areas of South Africa remains the most effective method in the prevention of late/end-stage disease. Continued research and the testing of novel abemaciclib-based combinations could create opportunities for reduction in cost and accessibility for South African women with mBC in both first and second-line settings.

Acknowledgments

Assistance with the study: The access to patient data and ethical support were obtained by the Wits Donald Gordon Medical Centre (Johannesburg, South Africa).

References

1. Global Burden of Disease 2019 Cancer Collaboration. Cancer incidence, mortality, years of life lost, years lived with disability and disability-adjusted years for 29 cancer groups from 2010 to 2019: a systemic analysis for the Global Burden of Disease Study 2019. JAMA Oncol 2022;8:420-444.
2. GBD 2017 Causes of Death Collaborators, Abate D, Abate KH. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-1788.
3. Sharma R, Aashima, Nanda M, et al. Mapping cancer in Africa: a comprehensive and comparable characterization of 34 cancer types using estimates from GLOBOCAN 2020. Front in Pub H 2022;10: 1-14.
4. Kakudji BK, Mwila PK, Burger JR, et al. Epidemiological, clinical and diagnostic profile of breast cancer patients treated at Potchefstroom regional hospital, South Africa: an open-cohort study. Pan African Med J 2020;36(9):1-11.
5. Mutebi M, Anderson BO, Duggan C, et al. Breast cancer treatment: A phased approach to implementation. Cancer 2020;126:2365-2378.
6. Roberto M, Astone A, Botticelli A, et al. CDK4/6 inhibitor treatments in patients with hormone receptor positive, HER2 negative advanced breast cancer: potential molecular mechanisms, clinical implications and future perspectives. Cancers (Basel) 2021;13:332.
7. Mayer EL. Targeting breast cancer with CDK inhibitors. Curr Oncol Rep 2015;17:443.
8. Denton E, Conron M. Improving outcomes in lung cancer: the value of the multidisciplinary health care team. J Multidisc Healthc 2016;9:137-144.
9. Avery M, Williams F. The importance of pharmacist providing patient education in oncology. J Pharm Pract 2015;28:26-30.
10. Krens SD, Lassche G, Jansman FGA, et al. Dose recommendations for anti-cancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019;20:e200-e207.
11. Verzenio-INN-Abemacilcib. European Medicines Agency. Available from: https//:www.ema.eur opa.eu/en/documents/product-information/verzenios-epar-product-information_en.pdf. Accessed November 12, 2022.
12. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31:1623-1649.
13. Meyer S, Nqabeni G. Cost of Cancer: Challenges for the Next 10 Years. 2021. https://canceralliance.co.za/wp-content/uploads/2021/08/Cost-of-Cancer-Advocacy-Report-V1.pdf. Accessed September 17, 2022.
14. Matilla O, Ahmad R, Hasan SS, Babar Z. Availability, affordability, access and pricing of anti-cancer medicines in low-income and middle-income countries: a systemic review of literature. Front in Pub H 2021;9: 1-13.