VOLUME - 11, ISSUE - 06, JUNE - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Oncology

EFFICACY OF PALBOCICLIB ON POSITIVE METASTATIC BREAST CANCE RECEPTOR, IN REAL WORLD DATA STUDIES AND OUR EXPERIENCE IN ONCOLOGY SERVICE

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ABSTRACT

BACKGROUND: Metastatic breast cancer is a burden on healthcare worldwide. Despite the progress made in early diagnosis and adjuvant treatment of breast cancer again about 30% of patients develop metastases in the course of their disease. Also, there is a percentage of patients where the disease presents in metastatic stage. Real-world data may provide valuable information on the effectiveness and safety of medicines, which is particularly relevant for clinicians, patients and third-party payers. **MATERIALS AND METHODS**: We have collected data from 63 patients at Mother Teresa Hospital receiving Palbociclib since June 2016 until October 2019. Patients aged≥18 years, diagnosed with ABC and exposed to Palbociclib plus Fulvestrant. Patients were followed-up until death. **RESULTS;** A total of 63 patients were included. Median age was 66 years (range 28–78) and 99.05% were female. Median follow-up time was 26.42 months. **CONCLUSION**: Palbociclib plus Lulvestrant seems an effective treatment for ABC in real-world context. Compared to registrations studies, as in the world practice, these medications are first line treatments in Albania as well, constituting a significant achievement in the fight against breast cancer.

KEYWORDS : breast cancer, Palbociclib, Fulvestrant, Real-world data, oncology services

INTRODUCTION

Breast cancer is the most common cancer and also the primary cause of mortality due to cancer in female around the World. About 1.38 million new breast cancer cases were diagnosed in 2008 with almost 50% of all breast cancer patients and approximately 60% of deaths occurring in developing countries.[1]

There is a huge difference in breast cancer survival rates worldwide, with an estimated 5-year survival of 80% in developed countries to below 40% for developing countries.[2] Metastatic breast cancer is a burden on healthcare worldwide. [3]

Despite the progress made in early diagnosis and adjuvant treatment of breast cancer again about 30% of patients develop metastases in the course of their disease. Also, there is a percentage of patients where the disease presents in metastatic stage. [4] In the last 2 decades of the last century research on breast cancer is focused on documenting and understanding biomarkers. [5]

New techniques such as IHC made this way of research possible by using highly specific antibodies against specific antigens such as hormone receptors (RH) or epidermal growth factor receptor (EGFR) suppressor tumor genes, adhesion factors and antiangiogenic, matrix metal proteases etc. of which some of them resulted in prognostic value.[6]

Nowadays, cancer analysis, whether for diagnosis or research purpose, using molecular morphological analysis of the tumor is made possible by the characterization of at least 4 distinct groups of breast cancer. Breast cancer cases are divided into 2 main groups that are well distinguished. One group showing low or absent ER expression and the second group where the gene responsible for the ER receptor is quite pronounced. [7]

Two distinct groups are described within the positive ER of breast cancer:

Luminal A where we have expressed Er and Pgr and GATA3 and Luminal B where we have low to moderate expression of ER, PGR and possibly a high Ki67. [8]

It is already clear that the high presence of ER especially in Luminal A correlates with better prognosis.

Also, the lack of ER and PGR creates 2 independent entities like:

- Triple negative (lack of receptor 2 of human epidermal growth factor (HER2) but high expression of cytokeratin (CK) characterized by a poor prognosis.
- HER2 positive subgroup with negative ER and PGR receptors (also with poor prognosis).[9]

Breast cancer positive and her2 negative hormones represent the most common form of breast cancer and consequently are the most common deaths from breast cancer.[7]

Blocking the hormonal pathway of cancer development has been the mainstay of treatment for decades. Endocrine therapy today represents the primary strategy for these metastatic patients. Hormone therapy is associated with a significant benefit in the majority of patients. [10]

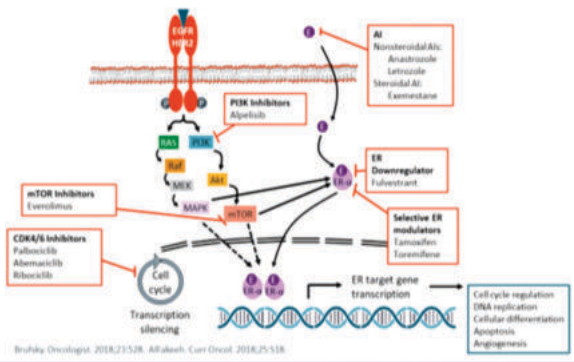

Figure 1 Combining Targeted and antiestrogen Therapies to Overcome Resistance in HR+ Advanced Breast Cancer

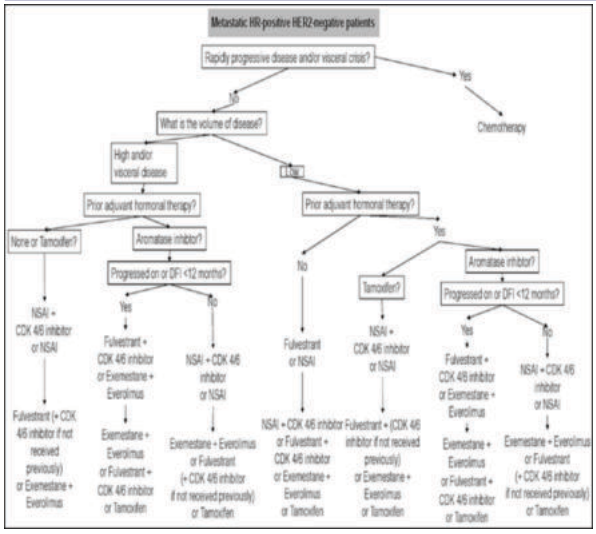

Figure 2 Treatment algorithm for patients with hormone receptor–positive, HER2 (human epidermal growth factor receptor 2)–negative metastatic breast cancer [11]

Despite treatment with hormonal therapies such as antiestrogens such as tamoxifen, aromatase nonsteroidal and steroidal inhibitors such as letrozole, anastrozole or exemestane in some patients show resistance to treatment which may be primary or acquired. [11]

Numerous randomized studies over the years have evaluated the role of e CDK4 /6 in cancer development and resistance to treatment. [12,13,14]

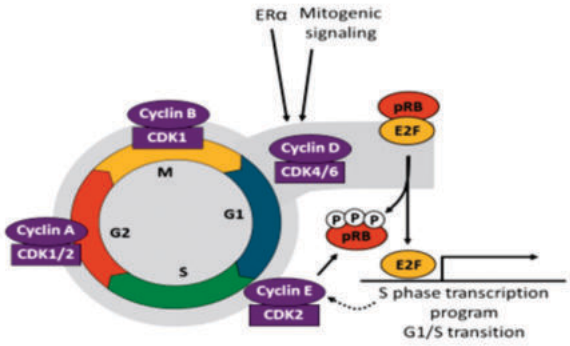

Figure 3 Role of CDK4/6 in Breast Cancer

The purpose of treating these patients is not to cure but to prolong survival and improve the quality of life. Randomized studies have already shown that the association of hormone therapy with a CDK4 / 6 inhibitor significantly increases PFS (the period without disease progression given in some cases as well as OS (overall survival).

Phase III Study	PALOMA-2[1,2]	MONALEESA-2[3,4]	MONARCH-3[5,6]	MONALEESA-3[7,8]	MONALEESA-7[9]
Setting	1st line	1st line	1st line	1st and 2nd line	1st line*
Endocrine partner	Letrozole	Letrozole	Letrozole or anastrozole	Fulvestrant	Tamoxifen, letrozole, or anastrozole
CDK4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Ribociclib
No. patients	666	668	493	365	672
HR	0.563	0.56	0.54	0.55	0.55
PFS, mos	27.6 vs 14.5	25.3 vs 16	28.18 vs 14.76	33.6 vs 19.2	23.8 vs 13.0
ORR, %	55.3 vs 44.4	52.7 vs 37.1	59 vs 44	40.9 vs 28.7†	41 vs 30

*1st line ET; up to 1 prior line of CT permitted in advanced setting (14% of patients had received CT in advanced setting). †Includes 1st and 2nd line.

Figure 4 Impact of CDK4/6 inhibition on PFS; First-line Setting

But randomized clinical trials investigate the benefits and harms of an intervention or treatment under highly controlled conditions and answer the question of whether a drug "works". [15-23]

Such studies have been created to show causality through the following features:

- The patient population is selected with strict inclusion and exclusion criteria and randomized. So, the patient has no concomitant diseases, takes other medications, has a very good performance.
- Treatment is protocol driven in a controlled "ideal environment"
- The intervention is implemented and standardized strictly and strictly
- Data are derived from protocol-defined endpoints, uniformly evaluated.

Real world data studies examine interventions or treatment in circumstances closer to real-world practice, with more heterogeneous patient populations, less standardized treatment protocols, and distribution in routine clinical settings. [16]

- Such studies are not able to determine causality and have the following characteristics:
- Patients are not random
- The general patient's population
- A wide range of important clinical measures and outcomes
- Routine clinical practice; the intervention is in the competence of the treating physician

The data derive from the clinical judgment of the doctor but also from the variability in patient care or even the commitment (adherence) of the latter.[17]

It is understood that both randomized and real-world data studies have their advantages and limitations.

The superiority of randomized studies lies in:

1. They have good study design with clear criteria
2. Randomization minimizes confounding factors and bias
3. They are blind which further minimizes bias
4. They are clear and easily understood

Their disadvantages are:

1. They are often associated with significant differences compared to the results in the real population

The purpose of the study (endpoint) focuses on some parameters such as Progression-free survival (PFS) or safety and neglects other aspects.

2. Difficulties in drawing conclusions in long term events
3. Thy are expensive and last in time

On the other hand, in Real World data studies [19]
A wider and more representative population can be estimated over a longer period of time, allowing:

1. Assessment of subpopulations and under-represented patients on RCT (including patients with comorbidities and co-medications)
2. Investigation of rare / long-term events or results
3. A wide range of important clinical measures and outcomes can be investigated, including questions that cannot be studied experimentally for ethical or financial reasons
4. The cost is relatively cheap compared to clinical trials and they can be performed in a shorter time frame.[20, 22]

However, RW studies also have their limitations, including:

1. Lack of chance and blindness
2. Higher risk of bias and the presence of confounding factors
3. Different levels of data availability and quality

4. Less standards about study models leading to a range of consistency between different studies

The data that come to us from the world experience, which means Real world data as the first line of treatment of the disease metastatic Palbociclib + LET is more effective than LET only in a heterogeneous population and among subgroups of different patients. [18-23]

These data complement the superior clinical efficacy observed with IBRANCE in randomized clinical trials. In the second part we will present our data on the efficacy of Palbociclib in the oncology hospital. Palbociclib has been reimbursed in Albania since 2016.

We have collected data from 63 patients at Mother Teresa Hospital receiving Palbociclib since June 2016 until October 2019.

Data came from patient files and records. In our study 63 patients received Palbociclib treatment. Most of patients have taken it together with letrozole. Only 5 patients have used the Fulvestrant combination Palbociclib due to the fact that Fulvestrant is still unreimbursed. In the table below are the characteristics of the patients

patient characteristic	PAL+ LET
Median age years 63pt	61,7 (27-75)
ECOG PS n (%)	
0	34 (54)
1	29(46)
Disease stage, n (%)	
IV	47(100)
Disease site n (%)	
Visceral	37(59)
Bone	24(38)
other	2 (3)
Disease free interval n (%)	
>12 month from adjuvant to recurrence	23(36)
	2-14y (6y)
<12 month from adjuvant to recurrence	20(31)
Metastatic from diagnosis	20(31)

Table 1 The data of the patients

From the follow up of our patients, the response to treatment was evaluated through parameters as objective response rate

characteristic	PAL + LET
Objective response rate	
Complete response n(%)	4 (6)
Parcial response n (%)	41 (65)
Stable disease	
Stable disease >1year	27 (42)
Stable disease <1year	12 (19)
Progresive disease<6months	18 (28)

Table 2 The data of the response patients after treatment

So, in 63 patients received the treatment. The most pronounced side effects were fatigue and leukopenia. Unlike chemotherapy this leukopenia due to its physio pathological mechanism is not associated with febrile situations.

Patients who respond best were 35 patients were still in treatment in October 2019. On average a patient has received 12.5 cycles of treatment (2-37) months, 23 patients have received more than 18 months of treatment which means significant period without advancement of their metastatic disease only with combined hormonal therapy.

From our data patients with bone, soft tissue and lung metastases have responded better to treatment.

In our study 23 patients have been metastatic since diagnosis most with bone metastases who received first-line treatment. This group has had the maximum benefit.

In other patients the greatest benefit from the treatment were the patients in whom the disease reappeared years after the initial diagnosis of cancer (2-14 years)

Patients who progressed; 26 patients have made disease progression under treatment. They have received an average of 8.8 months of medication (2-20 months) Only 9 out of 63 patients did not respond to treatment (received less than 3 months of treatment)

Most with hepatic metastases and short interval from previous hormonal treatment.

In conclusion we can say that even in our clinical practice the combined use of letrozole with CDK 4/6 inhibitor Palbociclib has doubled the disease-free period for metastatic patients with breast cancer hormone receptor positive and her 2 negatives.

As in the world practice, these medications are first line treatments in Albania as well, constituting a significant achievement in the fight against breast cancer.

CONCLUSIONS

Palbociclib plus Lulvestrant seems an effective treatment for ABC in real-world context. Compared to registrations studies, as in the world practice, these medications are first line treatments in Albania as well, constituting a significant achievement in the fight against breast cancer.

Declarations:

Competing interests

The authors declare that they have no competing interests.

Ethical Considerations:

Informed written consent from the patient included in this study was taken.

Consent for publication:

All authors read and approved the final manuscript.

Availability of data and material:

The data that support the findings of this study are available on request from the corresponding author.

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