Short Commentary

Incidence of neutropenia and effectiveness of palbociclib in clinical practice in metastatic breast cancer

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Background

Breast cancer is a frequent condition among Spanish women, being the number one in prevalence during 2018, representing 36.2% of all tumors affecting women, being one of the most frequent type of breast cancer the HR+/HER2- type.

Endocrine therapy has been the standard treatment of hormone receptor positive/HER2-negative breast cancer. However, the emergence of resistance mechanisms and more complex breast cancer subtypes has led to the development of targeted drugs that offer better health outcomes. These drugs belong to the family of cyclin-dependent kinase 4/6 inhibitors, among which palbociclib stands out as the first in its class. Palbociblib (Ibrance®), was authorized in Spain in 2016, and has become a new standard in the treatment of locally advanced or metastatic breast cancer, associated with an anti-estrogen drug. The PALOMA pivotal trials led to the authorization of the drug, studying the combination of palbociclib with letrozole (PALOMA-1 AND -2) and with fulvestrant (PALOMA-3). In the phase 3 trial (PALOMA-3) the combination of palbociclib plus fulvestrant yielded significantly superior results in both Progression-Free Survival (PFS) and Overall Survival (OS) compared to fulvestrant plus placebo. This treatment is generally well tolerated, with only neutropenia standing out as the most frequent adverse effect and the main reason for reducing the drug dose. More and more studies are evaluating the efficacy and safety of palbociclib in real life, however, in the Spanish population the results are still scarce. The Ibrance Real World Insights (IRIS) is a retrospective study of the use of palbociclib in its licensed indications in multiple countries in North America, South America and Europe.

Objective

This study evaluated the effectiveness and toxicity in real clinical practice of palbociclib combined with endocrine therapy for the treatment of metastatic or locally advanced breast cancer in any line.

Methods

We conducted a single-center retrospective study of all women with metastatic or locally advanced breast cancer treated with palbociclib, during a 3-year period (July 2016-August

2020) in a Spanish tertiary hospital (Hospital Clínico Universitario Lozano Blesa, Zaragoza).

Palbociclib was administered at the standard starting dose of 125 mg, for 21 days, followed by 7 treatment-free days. Dose reductions to 100 and 75 mg were not a reason for exclusion from the study.

Patients were identified using the Pharmacy Service dispensing program FarmaTools®. Information was obtained from medical records and laboratory reports, and hormone treatment from each patient's electronic prescription.

Neutrophil values were determined on day 1 and 15 of the first cycle and on the day of each dose reduction, classifying the presence of neutropenia into 4 grades according to the US National Cancer Institute's Common Toxicity Criteria.

In addition, data were collected on the presence of bone metastases at the start of palbociclib treatment, whether they had been treated with prior conventional chemotherapy (QT), and the line number at which palbociclib is initiated.

Progression-Free Survival (PFS) was defined as the time from initiation of palbociclib treatment to disease progression or death from any cause. On the other hand, Overall Survival (OS) was the time from initiation of CDK inhibitor to death from any cause. The Kaplan-Meier estimator was used to assess survival variables. Progression was defined by evidence of radiological progression or patient death.

Results

Patient characteristics

A total of 58 patients with metastatic or locally advanced breast cancer were included in the study. Median age at diagnosis was 55 years (range 28-84) and palbociclib initiation was 59.0 years (range 33-87). The median number of completed cycles was 9 (range 2-34).

The concomitant hormonal treatment of 50.0% was fulvestrant, 43.1% letrozole, 3.4% goserelin 1.7% anastrozole and 1.7% exemestane. 51.7% received palbociclib as firstline, 32.8% as secondline and 15.5% as successive lines of treatment.

Hematologic toxicity

The mean neutrophil count was reduced by 52.9%, from baseline to the middle of the first cycle, with neutropenia appearing in 69.0% of patients (1.7% grade 4; 22.4% grade 3; 24.2% grade 2, 20.7% grade 1). 44.8% [26] underwent a first level dose reduction to 100 mg, with neutropenia appearing in 92.3% of these (15.4% grade 4; 61.5% grade 3; 15.4% grade 2). Of the former 46.2% [12] required a further reduction to 75 mg, with neutropenia appearing in 91.6% (58.3% grade 3; 25% grade 2; 8.3% grade 1). Bone metastases were present in 44.8% [26] of the patients at the time of initiating treatment with palbociclib. The rest had metastases in another location or had not yet developed them.

Effectiveness and response

Prior to palbociclib 58.6% [34] of the patients had a chemotherapy line. Median Progression-Free Survival (PFS) was 17.6 (±1.8) months, 48.3% [28] experimented progression during the study.

The average overall survival was 25.7 (±1.3) months. From the 58 initial patients 24.1% [14] died during the study.

Patients who, for reasons of hematologic toxicity, required one or successive drug dose reductions, were not more likely to progress (p=0.196).

Conclusion

Metastatic breast cancer is the second most frequent cause of death in women in the world, being the cancer with the highest mortality in women in Spain. Treatment with hormone inhibitors had been the gold-standard treatment for women with metastatic breast cancer and positive hormone receptors. The CDK4/6 cyclin inhibitor palbociclib has rapidly become a standard of care for these patients, thanks to the favorable results shown by the PALOMA trials in terms of efficacy and toxicity.

Haematological toxicity in the form of neutropenia was frequent, from the first cycle, and remained despite successive dose reductions; reductions were needed in almost half of the patients. However, these dose reductions were not associated with an increased risk of progression. Bone metastasis is very common in metastatic or locally advanced breast cancer. Since the authorisation for first line use (PALOMA-2) it has become a standard of treatment for metastatic or locally advanced breast cancer.

Palbociclib is an effective and safe treatment option in patients with heavily pretreated endocrine-sensitive metastasic breast cancer, especially in those with longer PFS to previous endocrine therapy.

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