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Research Article

Efficacity of CDK 4/6 Inhibitors in Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer: Experience from the Medical Oncology Department at Hassan II University Hospital in Fez

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Abstract

CDK 4/6 inhibitors have represented a major advancement in the management of patients with hormone receptor-positive, HER2-negative metastatic breast cancer. However, their high cost and the difficulty in obtaining reimbursement make their use in routine practice a challenge for both physicians and patients.This cohort aims to present real-world data on the effectiveness of CDK 4/6 inhibitors.This is a non-comparative retrospective exposure cohort including all patients who received CDK 4/6 inhibitors at the oncology department of Hassan II University Hospital in Fez between January 2021 and June 2024. The primary objective was progression-free survival (PFS), and the secondary objective was disease-free survival. The Kaplan-Meier method was used, and mean survival rates were calculated with two-sided 95% confidence intervals (95% CI).During this period, we identified 27 patients who received CDK 4/6 inhibitors, with 85.2% on Palbociclib and 11.2% on Ribociclib. 63% received CDK 4/6 inhibitors as first-line treatment, and 37% after first-line treatment (chemotherapy, or hormone therapy alone with aromatase inhibitors or tamoxifen). 77.8% were sensitive to hormone therapy, 22.2% had secondary resistance, and none had primary resistance. The median survival was not reached for either PFS or overall survival. The mean PFS was estimated at 22.148 months (95% CI: [16.697−27.599 months]), and the mean overall survival was estimated at 25.543 months (95% CI: [24.384−26.702 months]).

Introduction

Breast cancer is the most frequent cancer in women worldwide, with an estimated 2 million new cases and 620 thousand deaths annually.1 Hormone receptor-positive (HR+) human epidermal growth factor receptor-2 negative (HER2–) tumors represent the most common subtype of the disease and is responsible for the majority of breast cancer deaths.2 In this subgroup of metastatic breast cancer (MBC), endocrine therapy (ET) remains the mainstay of treatment. International guidelines such as those from American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and Advanced Breast Cancer (ABC4) clearly

state that ET should be considered the preferred first-line therapy for these patients in the absence of very symptomatic visceral disease or evidence of endocrine resistance.

Furthermore, all guidelines recommend sequential lines of ET delaying chemotherapy (CT), whereas clinical characteristics allow for available hormonal approaches. Although compliance with guidelines in general do vary significantly for many different reasons and according to practice settings worldwide, in this situation, we could expect a substantial impact in patient quality of life whether patients are treated with CT or ET. The use of data from real-world clinical practice to explore clinical and policy-relevant questions is gaining increased interest. Indeed, data from cancer registries and linked treatment records can provide unique insight into patient treatment and outcomes in routine oncology practice.3 The objective of this article was to evaluate real-world data (RWD) regarding the patterns of first-line treatment of HR+ HER2– MBC with a special focus on the use of CT in this setting, and the potential implications and perceived preliminary changes after the introduction of CDK4/6 inhibitors will also be addressed. This cohort aims to present real-world data on the effectiveness of CDK 4/6 inhibitors.This is a non-comparative retrospective exposure cohort including all patients who received CDK 4/6 inhibitors at the oncology department of Hassan II University Hospital in Fez between January 2021 and June 2024.

Results

The primary objective was progression-free survival (PFS), and the secondary objective was disease-free survival. The Kaplan-Meier method was used, and mean survival rates were calculated with two-sided 95% confidence intervals (95% CI).

During this period, we identified 27 patients who received CDK 4/6 inhibitors, with 85.2% on Palbociclib and 11.2% on Ribociclib. 63% received CDK 4/6 inhibitors as first-line treatment, and 37% after first-line treatment (chemotherapy, or hormone therapy alone with aromatase inhibitors or tamoxifen). 77.8% were sensitive to hormone therapy, 22.2% had secondary resistance, and none had primary resistance. The median survival was not reached for either PFS or overall survival. The mean PFS was estimated at 22.148 months (95% CI: [16.697−27.599 months]), and the mean overall survival was estimated at 25.543 months (95% CI: [24.384−26.702 months]).

Discussion

Very consistently, observational studies show that until recently, and despite international guidelines recommendations, a significant number of patients with HR+ HER2– MBC received CT as their first-line

treatment. This finding, although surprising, has significant consequences in patients, which reported toxicity and quality of life without clear benefit in terms of disease outcome. Of note, one of the bases of first-line ET recommendation is based on a meta-analysis comparing old CT versus ET agents with a limited statistical power.23 In addition, clinical situations were not well described by the meta-analysis and published studies, such as early relapse under adjuvant ET, low estrogen-receptor score, visceral crisis and symptomatic lesions, and cancer burden, which might explain decisions on first-line treatment. Although we could not find a detailed analysis of the potential reasons for this deviation from expert suggestions and prevailing guidelines, a number of possible explanations can be considered. Misconceptions regarding the clinical impact of visceral metastases, which are seen in a significant number of patients with HR+ MBC, and unclear existing definitions of visceral crises certainly play an important role leading some physicians to recommend CT for these patients. The perception of better outcomes related to CT is another misunderstanding underlying the decision away from ET in this setting. Nonetheless, a phase III trial recently showed that circulating tumor cells (CTCs) count may be a reliable biomarker method for guiding the choice between CT and ET (CT if ≥ 5 CTCs/7.5 mL; ET if < 5 CTCs/7.5 mL) as first-line treatment in HR+ HER2– MBC to achieve a similar PFS benefit.24 Physician local practices and institutional recommendations resulting in prescription of CT in certain settings should also be considered and is probably a factor in some regions of the world. Access and reimbursement issues do also play a role as discrepancies in availability of many new agents represent an ongoing challenge with impact on treatment selection that influence care patterns in health systems world wide. A recent network meta-analysis25 incorporating information from the last 2 decades of research clearly indicates that ET, particularly incorporating the modulation of single-agent endocrine approaches with targeted drugs (CDK4/6 inhibitors, mTOR inhibitors, PIK3CA inhibitors), does represent the best approach resulting in better outcomes for these patients. Moreover, the avail able information regarding the toxicity associated with all the available regimens indicates that it is preferable to delay CT administration in line with the recommendation of sequencing ET as long as there is no suggestion of endocrine resistance or visceral crises. Of note, the efficacy of some of these new ET combination regimens has not been tested in visceral crises as these patients have been excluded from recent clinical trials. Furthermore, the few recently available comparative trials (PEARL, BOLERO-6) do not address this specific first-line setting population and thus this important issue remains a challenging research question. These 2 recent randomized studies address the comparison of combination of ET plus palbociclib (PEARL) or ET plus everolimus (BOLERO-6) with CT in patients with HR+ MBC that progressed to prior ET, and fail to show an advantage with CT in terms of PFS while reporting higher toxicity.26,27 The YOUNG PEARL trial included premenopausal women and compared ET (exemestane with gonadotropin-releasing

hormone agonist) plus CDK 4/6 inhibitor versus CT and showed a PFS benefit compared with CT. Fifty percent of patients were treated in first-line setting and in a subgroup analysis these patients also showed a trend, nonstatistically significant, toward ET benefit.28 In general, other than considering the different outcomes reported in some of the analysis from our review, deviations from treatment guideline recommendations may also have important implications on health care costs.29 Despite a lack of survival benefit, concordant care is associated with lower costs, suggesting potential benefit to increasing standardization of care.30 Nonconcordant treatment is associated with higher health care utilization and costs, with mortality differences observed by the type of guideline deviation.31 CDK 4/6 inhibitors in combination with ET were approved just recently for use in first-line setting in the United States Food and Drug Administration (FDA) and Europe European Medicines Agency (EMA): 2015 palbociclib, 2017 ribociclib, and 2018 abemaciclib. The consistent benefits in terms of PFS and OS with CDK 4/6 inhibitors in first- and second-line settings are changing clinical practice. Recent data from the United States indicate that the scenario of high utilization of CT in first-line HR+ MBC could be changing with the introduction of CDK4/6 inhibitors. According to this very timely preliminary analysis, only a minority of patients received first-line CT in the first semester of 2017, most others receiving different forms of ET.17 A recent study in Germany showed that CDK4/6 plus ET use increased from 38.5% to 62.7% in the first 2 years after CDK4/6 inhibitor treatment became available since November 2016, whereas CT and ET monotherapy use decreased from 2015 to 2018 from 42.2% to 27.2% and from 53% to 9.5%.32 One added comment to consider is that even though CDK4/6 inhibitors may actually change practice, as emerging evidence suggests, in most parts of the world, access problems will restrict significantly availability of these agents, and as a consequence most patients will continue to be managed as documented in our review. Finally, disparities in access to these new agents will certainly remain an issue and influence practices and outcomes worldwide. RWD studies in different regions of the globe will certainly be informative identifying differences in ongoing clinical practice and barriers to optimal care to be addressed. In particular, a significant issue for most markets around the world, the PEARL trial brings a challenging conclusion that may influence practice in different ways. Although the basic objective of the trial was to demonstrate that ET plus CDK 4/6 inhibitor is the preferred alternative in patients with ER+ HER2– MBC who progressed to ET, it showed that capecitabine is associated with similar outcomes, albeit with higher toxicity. Nevertheless, capecitabineis probably more widely available and, importantly, cheaper for most health care systems worldwide. Therefore it is reasonable to consider that this fact will have a significant role in managing decisions in the current treatment scenario.

Conclusion

Although the survival data are still immature and the use of CDK 4/6 inhibitors was outside the eligibility criteria in Paloma 2, Paloma 3, Monaleesa 2 and Monaleesa 3, a significant benefit was observed in our patients, highlighting the need to continue advocating for the democratization of access to these new targeted therapies.

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