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Palbociclib or Ribociclib in First-Line Treatment in Patients With Hormone Receptor—Positive/Human Epidermal Receptor 2—Negative Advanced or Metastatic Breast Cancer? A Perspective Based on Pharmacologic Costs

Abstract

Purpose: To assess the pharmacologic costs of CDK4/6 inhibitors (palbociclib and ribociclib) in hormone receptor—positive (HR^+)/human epidermal receptor 2—negative ($HER2^-$) advanced or metastatic breast cancer (BC). Pivotal phase 3 randomized controlled trials (RCTs) were considered. **Discussion:** Two phase 3 RCTs including 1334 patients were considered. European Society for Medical Oncology Magnitude of Clinical Benefit Scale reached grade 3 for the PALOMA-2 and MONALEESA-2 trials. Pharmacologic costs of palbociclib and ribociclib at full dose were similar, at €3864 and €4002 per month of progression-free survival (PFS) gained, respectively. The reduction of dose of ribociclib (36.1% in the pivotal RCT vs. 36.0% of palbociclib in pivotal RCT) resulted in €2718 and €1348 per month of PFS gained at 400 and 200 mg daily, respectively. **Conclusion:** When pharmacologic costs of drugs are combined with the measure of efficacy represented by PFS, both palbociclib and ribociclib are cost-effective first-line treatments in postmenopausal women with $HR^+/HER2^-$ advanced or metastatic BC, with a lower cost in favor of ribociclib in patients with dose reduction.

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Keywords: CDK4/6 inhibitors, Clinical benefit, Cost of drugs, Phase III randomized controlled trials, Progression-free survival

Introduction

The introduction of CDK4/6 inhibitors for the first-line treatment in postmenopausal women with hormone receptor—positive (HR^+)/human epidermal receptor 2—negative ($HER2^-$) advanced or metastatic breast cancer (BC) is associated with a relevant increase in costs, and it might be interesting to strike a balance between the costs of these new treatments (palbociclib, ribociclib) and the added value represented by the improvement of the clinical parameters of interest such as progression-free survival (PFS).

We conducted an analysis to assess the pharmacologic costs of poly(ADP-ribose) polymerase inhibitors (palbociclib and ribociclib) in $HR^+/HER2^-$ advanced or metastatic BC. Pivotal phase 3 randomized controlled trials (RCTs) of palbociclib and ribociclib in $HR^+/HER2^-$ advanced or metastatic BC were considered; the last available update of each trial was considered as the original source. Differences in PFS (expressed in months) between the different arms were calculated and compared to the pharmacologic costs (at our hospital pharmacy; expressed in euros) needed to obtain 1 month of PFS.

We assumed the following costs for each month of therapy: palbociclib = €1980 at 125 mg daily (125 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles; same price for 100 mg and 75 mg daily), ribociclib = €1862.31 at 600 mg daily (600 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles), ribociclib = €1251.54 at 400 mg daily (400 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles), and ribociclib = €620.77 at 200 mg daily (200 mg per day on a 3-weeks-on, 1-week-off schedule in 28-day treatment cycles). The dosage of drugs were considered according to those reported in each RCT.

We subsequently applied the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) to the phase 3 RCTs[1] we studied to derive a relative ranking (from grade 1 to grade 5) of the magnitude of clinically meaningful benefit that can be expected in this setting; adjustments (upgrade or downgrade) are planned on the basis of quality of life or grade 3/4 toxicities affecting daily well-being.

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Discussion

Two phase 3 RCTs including 1334 patients were considered.[2,3] The main reported outcomes of the analyzed phase 3 RCTs are listed in Table 1. ESMO-MCBS reached grade 3 for both the PALOMA-2 trial[2] and the MONALEESA-2 trial.[3,4] Combining the costs of therapy with the measure of efficacy represented by the PFS, we calculated the costs for obtaining the advantage in PFS for each arm of the analyzed trials. Pharmacologic costs of palbociclib and ribociclib (full dose, 63.9% in the pivotal RCTs[3]) were similar, at €3864 and €4002 per month of PFS gained, respectively. The reduction of dose of ribociclib (36.1% in the pivotal RCT[3] vs. 36.0% of palbociclib in the pivotal RCT[2]) resulted in €2718 and €1348 per month of PFS gained at 400 and 200 mg daily, respectively. The price was the same for palbociclib both at full dose and with dose reduction.

From the data presented, it is easy to see that the pharmacologic costs were influenced by two main factors: the efficacy of the therapies (strictly associated with patient inclusion criteria) and the drug price. We decided to limit our evaluation to phase 3 RCTs because phase 2 trials looking for effective combinations are plagued by patient selection biases that significantly reduce the possibility to define credible measures of efficacy (ie, PFS). Furthermore, we needed randomized trials to allow comparison of efficacy between the arms of each trial.

Despite this, our analysis has several limitations, such as cross-trial comparisons. To this must be added the fact that there is no informations concerning the extension of the estimated costs to the overall survival (OS) benefit. Moreover, the use of PFS and OS is unconventional but raises interesting issues. It is true that the classical incremental cost-effectiveness ratios, reporting as PFS or OS per life-year and quality-adjusted life-year, better convey how much the treatment itself contributes to overall costs toward conventional cost-effectiveness analyses,[5] but this method also has several limitations. The first concerns the controversy in using PFS or OS. Indeed, the use of OS as an estimate for life-year is a complicated end point to model, while the use of PFS will likely underestimate the life-years saved.[6] Second, the use of sensitivity analyses that incorporate different ranges of variables could lead to a certain amount of probability of misinterpreting the cost-effectiveness of different agents in the treatment of advanced cancer. The use of PFS therefore allows us to obtain a quick measure of effectiveness that permits us to calculate the costs of different therapies in first-line therapy as well as in daily clinical practice.[7]

Although we have considered only the direct costs, there are other important cost elements that are not considered here, including outpatient/inpatient administration costs, costs of treatment-related adverse events, and health-related quality of life between different first-line treatments. In fact, the data we report do not comprise a real cost-effectiveness analysis (that would imply not only direct medical costs but also indirect medical costs) but rather an analysis of pharmacologic costs. We also know the limits of completeness of this cost analysis, which does not consider the toxicity of the different schemes because that implies a different analysis. In particular, in the pivotal phase 3 RCTs, serious adverse events occurred in 19.6% in the palbociclib/letrozole group[2] versus 12.6%

Table 1 Pharmacologic Costs and Difference in PFS With CDK4/6 Inhibitors in Pivotal Phase 3 RCTs in Refractory Hormone Receptor–Positive Advanced Breast Cancer

Trial	Comparative Regimen	Total No. of Patients	Primary End Point	ORR (%)	*P*	PFS (Months)	*P*	OS (Months)	*P*	PFS Gain (Months)	PFS HR (95% CI)	ESMO-MCBS	Median Duration of Treatment (Months)	Costs of Therapy (€)	Difference in Costs (€)	Difference in Costs Per Month of PFS Gained (€)
PALOMA-2[2]	Palbociclib + letrozole	444	PFS	42.1	NS	24.8	<.001*	NM	NA	10.3	0.58 (0.46-0.72)	3	20.1	*x* + 39,798	39,798	3864
	Placebo + letrozole	222		34.7		14.5		NM					14.0	*x*		
MONALEESA-2[3]	Ribociclib + letrozole	334	PFS	42.5[a]	<.001*	25.3[a]	<.001*	NM	NA	9.3	0.56 (0.43-0.72)	3	20.2[a]	*x* + 37,219[b] *x* + 25,281[c] *x* + 12,540[d]	37,219[b] 25,281[c] 12,540[d]	4002[b] 2718[c] 1348[d]
	Placebo + letrozole	334		28.7[a]		16.0[a]		NM					14.1[a]	*x*		

Abbreviations: ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (from grade 1 to grade 5); NA = not applicable; NM = not mature; NS = not significant; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
[a]Updated results of MONALEESA-2.[4]
[b]For patients without dose reduction.
[c]For patients with dose reduction at 400 mg.
[d]For patients with dose reduction at 200 mg.
*Statistically significant ($P < .05$).

in the placebo/letrozole group in the PALOMA-2 trial,[2] and in 21.3% in the ribociclib/placebo group versus 11.8% in the placebo/letrozole group in the MONALEESA-2 trial.[3] In addition, the annual cost of drug treatment (€46,368 for palbociclib[2] and €48,024 for ribociclib[4]) are in line with those reported in literature, which found a favorable implementation intervention for thresholds of less than $61,500 per life-year gained.[8] The pharmacologic costs are transferred to the reality of the Italian context, and more generally to Europe thanks to the free movement of patients and goods. The idea is to emphasize not only the cost but also the method, which is to combine the pharmacologic costs of drugs with measures of efficacy (PFS, OS) in order to achieve a given objective as possible. This method incorporates a structured, rational, and valid approach to data interpretation and analysis that can help clinicians weigh the relative merits of competing relevant therapeutic options in situations where there is no direct comparative data comparing the available therapeutic options.[1] Further, the use of ESMO-MCBS to standardize the scientific validity may be criticized, as there is a lack of consideration of toxicities in the definition of the grade of magnitude of clinical benefit.

However, to our knowledge, ours is the first analysis of the pharmacologic costs of CDK4/6 inhibitors, such as palbociclib and ribociclib, in the treatment of $HR^+/HER2^-$ advanced or metastatic BC that is linked to PFS.

Conclusion

When the pharmacologic costs of drugs are combined with the measure of efficacy represented by PFS, both palbociclib and ribociclib are cost-effective first-line treatments in postmenopausal women with $HR^+/HER2^-$ advanced or metastatic BC, with a lower cost in favor of ribociclib in patients with dose reduction (about 36.0% of patients) and with a mean savings of 14.6% every 100 patients treated with ribociclib versus palbociclib (from 8.0% to 21.2%), confirming data from different countries.[9-11]

The price of newly registered oncologic drugs is continuously increasing, posing a serious threat to the sustainability of national health systems, especially in countries with limited public control and oversight over drug prices. Medical oncologists, and society as a whole, are becoming increasingly concerned with the issues of the costs of curing cancer. Attention must be brought to the just price of new treatments that must reflect the reality of their true benefits as well as their societal and personal costs.

Disclosure

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

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