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ORIGINAL ARTICLE

Cost-effectiveness of palbociclib in hormone receptor-positive advanced breast cancer

H. Mamiya[1], R. K. Tahara[2], S. M. Tolaney[2], N. K. Choudhry[3] & M. Najafzadeh[3*]

[1]Department of Health Policy and Management, Harvard T.H. Chan School of Public Health, Boston; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston; [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham & Women's Hospital, Harvard Medical School, Boston, USA

Correspondence to: Dr Mehdi Najafzadeh, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02120, USA. Tel: +1-617-278-0930; E-mail: mnajafzadeh@bwh.harvard.edu

Background: Palbociclib (PAL), a novel small-molecule inhibitor of cyclin-dependent kinases 4 and 6 for the treatment of advanced breast cancer, has demonstrated significant efficacy in prolonging progression-free survival when added to existing therapies. Considering the high cost of PAL, we assessed cost-effectiveness of adding PAL to usual care in treatment of advanced breast cancer.

Methods: We developed a discrete event simulation model to simulate time to cancer progression and to compare life time clinical benefit and cost of alternative treatment strategies for patients with metastatic disease from societal perspective. Per approved indication, endocrine treatment naive patients were assigned to PAL plus letrozole (PAL + LET) or letrozole alone (LET). Patients with prior endocrine therapy were assigned to PAL plus fulvestrant (FUL) (PAL + FUL) or FUL alone. The model assumptions were informed based on published clinical trial data and other peer reviewed studies. We carried out one-way and probabilistic sensitivity analyses to assess the robustness of our results to the changes in model assumptions.

Results: In treatment-naive patients, the addition of PAL to LET cost an estimated $768 498 per additional quality-adjusted life-year (QALY) gained. The addition of PAL to FUL in patients with prior endocrine therapy cost an estimated $918 166 per QALY gained. Sensitivity analyses demonstrated adding PAL has a 0% chance of being cost-effectiveness in either patient groups at a willingness-to-pay threshold of $100 000 per QALY.

Conclusion: From a societal perspective, PAL treatment of both patient groups (with and without prior endocrine therapy) is highly unlikely to be cost-effective compared with the usual care in the USA.

Key words: cost-effectiveness analysis, cost utility analysis, economic evaluation, breast cancer, palbociclib

Introduction

Breast cancer is the most common cancer among women worldwide, with ~1.7 million cases reported each year [1]. Pharmacological therapy for breast cancer is generally decided based on the status of hormone (estrogen and progesterone) receptors and human epidermal growth factor receptor 2 (HER2) expression. Endocrine therapy plays a considerable role in initial management of patients with hormone receptor-positive advanced breast cancer. However, patients eventually develop resistance to such treatments [2–5]. Palbociclib (PAL) is novel cyclin dependent kinases 4 and 6 (CDK4/6) inhibitor that was approved as a first-line endocrine therapy, in combination with letrozole (LET), for postmenopausal women with hormone-receptor-positive, HER2-negative advanced breast cancer in 2015, and this year was approved to be used in combination with fulvestrant (FUL) for women with hormone-receptor positive, HER2-negative advanced breast cancer with disease progression following endocrine therapy [6].

In the open-label, phase 2, PALOMA1 study, patients assigned to PAL plus LET (PAL + LET) as first-line treatment had a significantly longer median progression-free survival (PFS) [20.2 months; 95% confidence interval (CI), 13.8–27.5] compared with LET alone (LET) (10.2 months; 95% CI, 5.7–12.6) [7]. In addition, PALOMA3, a phase 3 study in patients with relapse or progression during prior endocrine therapy, reported a median PFS of 9.2 months (95% CI, 7.5–not estimable) in the PAL plus FUL (PAL + FUL) group versus 3.8 months (95% CI, 3.5–5.5) in the FUL alone (FUL) group [8].

Despite the substantial clinical benefit, utilization of PAL at the current prices of ~$10 000 per month can result in substantial increase in treatment costs in the near future [9]. The only published cost-effectiveness conducted in Switzerland suggests that addition of PAL to LET does not seem to be cost-effectiveness in treatment-naive patients at current prices [10]. To date, no study has evaluated the cost-effectiveness of PAL compared with current endocrine therapies in the context of US health care. Therefore, we conducted a cost-effectiveness analysis of adding PAL compared with usual care in the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer in the USA.

Methods

We developed a discrete event simulation (DES) model using Arena, version 14.70 (Rockwell Automation, Inc., Milwaukee, WI) to simulate the time to cancer progression for each line of treatment and the time to death among postmenopausal women with ER-positive, HER2-negative advanced breast cancer and compared clinical benefits and cost of alternative treatment strategies (supplementary Figure S1, available at *Annals of Oncology* online). Individual patients were tracked throughout their life time and quality-adjusted life-years (QALYs) they gained and costs accrued were recorded. We used DES to model heterogeneities in baseline characteristics and patients' treatment histories. These are distinct properties of DES approach that allow modeling the impact of individual level variables on event probabilities and health state trajectories in the simulation.

Patients and intervention

We created a hypothetical cohort of 10 000 patients with the baseline characteristics similar to those observed in previous clinical trials (Table 1). We generated identical clones of each patient and assigned them to alternative treatment strategies. We considered two groups of breast cancer patients in our analysis: treatment naive patients and patients with prior endocrine therapy.

Intervention for treatment-naive patients. Treatment-naive patients were assigned to PAL (125 mg/day for 3 weeks, followed by 1 week-off) plus LET (2.5 mg daily) or LET as first-line endocrine therapy. These patients also received the following subsequent therapies: FUL (500 mg every 14 days for the first 3 injections and then every 28 days) as second-line endocrine therapy, everolimus (10 mg daily) plus exemestane (25 mg daily) as third-line endocrine therapy, and three lines of chemotherapy, according to National Comprehensive Cancer Center Network guidelines [11, 12]. Treatment naive patients who were assigned to PAL also required additional laboratory tests on day 14 of the first two cycles, in addition to usual tests at the beginning of each cycle.

Intervention for patients with prior endocrine therapy. Patients with prior endocrine therapy were assigned to PAL + FUL or FUL, followed by everolimus plus exemestane and three lines of chemotherapy, at the same doses as treatment naive patients. Patients in each group were allowed to change chemotherapy regimen without further rounds of endocrine therapy or stop any subsequent therapy during the course of treatment.

Disease progression

Model assumptions regarding disease progression, adverse events, and associated mortality rates are presented in Table 1. PFS time was defined as the time until disease progression or death after treatment initiation. The hazards of disease progression on treatment with each of the endocrine therapies were derived from PFS curves reported by published randomized clinical trials [7, 8, 13]. A published observational study was used to calculate the hazards of disease progression for chemotherapy [14]. Rates of adverse events, including febrile neutropenia, were based upon previous clinical trials [7, 8, 13, 15]. We assumed the risk of adverse events to be constant regardless of PFS time. A mortality rate of 3.6% for febrile neutropenia was used based on a previously reported longitudinal discharge database [16]. The additional length of hospital stay due to adverse events was also derived from the same studies [15, 16]. After disease progression, patients could move to the next lines of therapy or stop further treatment (supplementary Figure S1, available at *Annals of Oncology* online). The proportion of patients who received subsequent therapies after disease progression was derived from previous observational and randomized studies that reported distribution of second-line therapy choices in advanced breast cancer patients [14, 17]. We assumed that 62% of patients with no further treatment elected to use a hospice for end-of-life care [18, 19]. Mortality rates for patients that did or did not receive hospice-based end-of-life care were derived from a retrospective study of the Medicare database [18–20]. The background mortality rate for women was derived from U.S. life tables published as part of National Vital Statistics Reports [21].

Costs and utilities

We included direct costs of medications, outpatient physician visits, laboratory tests, hospice stays, and adverse events in our model. All drug costs were based on wholesale acquisition costs [22]. Costs of outpatient physician visits, laboratory tests, computed tomography scans, and bone scans were based on the Medicare physician fee schedule [23]. A previous cost-effectiveness study of advanced breast cancer and a separate retrospective study were used to estimate the costs of adverse events, hospice stays, and the cost of death outside a hospice [16, 19, 24, 25]. The costs of grade 1 (mild) or 2 (moderate) adverse events [defined according to Common Terminology Criteria for Adverse Events (CTCAE)] were not considered in the present analysis. Where appropriate, costs were adjusted for inflation to reflect 2015 US dollars using the US consumer price index [26]. The peer-reviewed literature were used to estimate the utilities associated with each health state (Table 1) [19, 27–31]. QALYs gained by individual patients were calculated by combining health state utility value and the time spent in that particular health state, before transitioning to subsequent health state. We assumed that utilities during endocrine therapy or chemotherapy were constant regardless of the number of treatment lines as long as patients experience PFS. A discount rate of 3% per year was applied to both costs and QALYs in accordance with US Public Health Service guidelines for cost-effectiveness analyses [32].

Sensitivity analysis

We carried out one-way sensitivity analyses by varying input parameters one at the time to explore the effects of changing our model assumptions (Table 1). Furthermore, we conducted a probabilistic sensitivity analysis by changing all model parameters at the same time [33]. For this purpose, we drew 10 000 sets of input parameters from their probability distributions and simulated the results in a cohort of 10 000 hypothetical patients for each parameter set. Incremental cost-effectiveness scatterplots and acceptability curves were generated from the results of the probabilistic sensitivity analysis.

Results

Model validation

Simulated clinical outcomes in our model were consistent with the results of targeted clinical studies in terms of overall survival (OS) and PFS (supplementary Figures S2 and S3, available at

Table 1. Model parameters and assumptions

Input parameter	Mean[a] (range)		Distribution	Reference
	For first-line indication	For second-line indication		
Progression free survival (month)				
Endocrine therapy			Weibull (scale, shape)	
First-line endocrine therapy				[7]
LET	10.2	–	Weibull [β (17, 209), 1.03]	
PAL+LET	20.2	–	Weibull [β (17, 1051), 0.80]	
Second-line endocrine therapy				[8]
FUL		3.8	Weibull [β (30, 90), 1.30]	
PAL+FUL	–	9.2	Weibull [β (40, 1021), 0.75]	
Third-line endocrine therapy				[13]
EVE/EXE		10.6	Weibull [β (93, 3011), 0.74]	
Chemotherapy			Hazard rate=λ	[14]
First-line chemotherapy		7.1	$\lambda = \beta$ (6, 53)	
Second-line chemotherapy		3.7	$\lambda = \beta$ (7, 30)	
Third-line chemotherapy		3.3	$\lambda = \beta$ (12, 46)	
Mortality rate				[16, 18–21]
No further treatment (per month)		0.50	β (25, 25)	
Hospice (per month)		0.48	β (24, 26)	
FN		0.04	β (98, 2624)	
Background mortality	0.00003 * exp(0.0924 * age)			
Incidence of adverse event				
Any grade 3 or 4 event				
LET	0.21	–	β (17, 64)	[7]
PAL+LET	0.77	–	β (64, 19)	[7]
FUL		0.18	β (31, 140)	[8]
PAL+FUL	–	0.69	β (239, 106)	[8]
EVE/EXE		0.50	β (239, 243)	[13]
Chemotherapy		0.38	β (95, 156)	[15]
FN (febrile neutropenia)				
FUL		0.01	β (1, 171)	[8]
PAL+FUL	–	0.01	β (2, 345)	[8]
Chemotherapy		0.13	β (33, 218)	[15]
Length of stay (day)				
Any grade 3 or 4 event		6	Normal (6, 4)	[15]
FN		8	Normal (8, 1)	[16]
Cohort characteristics				
Baseline age distribution		64	Normal (64, 10)	[7]
Proportion of receiving subsequent therapy				[14, 17–19]
Second-line endocrine therapy from first-line endocrine therapy	0.54	–	β (180, 151)	
Third-line endocrine therapy from second-line endocrine therapy		0.42	β (75, 105)	
First-line chemotherapy from any endocrine therapy in usual care		0.87	β (87, 13)	
First-line chemotherapy from any endocrine therapy in PAL+LET users	0.53	–	β (257, 228)	
First-line chemotherapy from any endocrine therapy in PAL+FUL users	–	0.77	β (77, 23)	
Second-line chemotherapy from first-line chemotherapy		0.64	β (234, 133)	
Third-line chemotherapy from second-line chemotherapy		0.68	β (160, 74)	
Hospice		0.62	β (132 064, 80 258)	
Utility				[19, 27–31]
Endocrine therapy	0.70 (0.5–1.0)		β (35, 15)	
Chemotherapy	0.58 (0.4–0.9)		β (29, 21)	
Toll for major toxicity	−0.28		β (14, 36)	
FN	0.47		β (23, 26)	
Hospice	0.48		β (24, 26)	
Terminal disease	0.23		β (12, 40)	

Continued

Table 1. *Continued*

Input parameter	Mean[a] (range)		Distribution	Reference
	For first-line indication	For second-line indication		
Unit cost (adjusted to 2015)				
LET/4 week	$655	–	γ (100, 7)	[22]
FUL/4 week	$1845[b]		γ (100, 18)	[22]
PAL/4 week	$9850 (500–10 000)		γ (100, 99)	[22]
EVE/4 week	$11 265		γ (100, 113)	[22]
EXE/4 week	$717		γ (100, 7)	[22]
Chemotherapy/month	$4741		γ (100, 47)	[25]
Outpatient physician visit/one time	$130		γ (36, 4)	[23]
Lab test/one time	$14		γ (13, 1)	[23]
CT scan (chest/abdomen/pelvis)/one time	$468		γ (14, 34)	[23]
Bone scan/one time	$178		γ (3, 56)	[23]
Hospice cost/month	$2698		γ (185, 15)	[19]
Toll for major toxicity/one time	$2131		γ (2, 1201)	[19, 25]
FN/one time	$17 052		γ (1177, 14)	[16]
Toll for death outside hospice/one time	$3216		γ (127, 25)	[24]

[a]Median value for the progression free survival inputs.
[b]Per 2 week cost for first three injections.
LET, letrozole; PAL, palbociclib; FUL, fulvestrant; EVE, everolimus; EXE, exemestane; FN, febrile neutropenia.

Annals of Oncology online). Although the PALOMA3 study did not report OS in either the PAL + FUL or FUL group, the median OS time of 25.0 months for FUL users who had relapsed or progressed during prior endocrine therapy, estimated by our model, matched the median OS time of 25.1 months reported in a previous clinical trial of FUL 500 mg [34]. The modelled cost of usual care ($128 435 US dollars in 2015) was similar to a SEER-Medicare data analysis that reported a mean lifetime cost of metastatic breast cancer of $109 923 in 2008 dollars (or $121 009 US dollars in 2015) [35].

Endocrine treatment-naive patients

The results of the base-case analysis comparing the usual care (LET) with PAL + LET are presented in Table 2. The average quality-adjusted life expectancy was 1.82 QALYs, with an average lifetime expenditure of $128 435 among LET users. PAL + LET users had a quality-adjusted life expectancy of 2.13 QALYs, with a lifetime expenditure of $372 761. Therefore, compared with the usual care, PAL + LET cost $768 498 per additional QALY gained. The results of one-way sensitivity analysis suggest that unit costs and health state utilities in our model had large effects on incremental cost-effectiveness ratios (supplementary Figure S4, available at *Annals of Oncology* online). Reducing the cost of PAL by 50%, 75%, and 90% would result in $367 459, $155 003, and $37 443 per additional QALY gained, respectively (Table 2). Our probabilistic sensitivity analysis demonstrated a 0% chance of PAL being a cost-effectiveness strategy unless we reach to a willingness-to-pay threshold of $250 000 per QALY gained (supplementary Figure S5, available at *Annals of Oncology* online). At 25% of the current PAL price, PAL + LET has a 26% probability of being the optimal strategy at a willingness-to-pay threshold of $100 000 per QALY.

Patients with prior endocrine therapy

Under the usual care (FUL), the quality-adjusted life expectancy in patients with prior endocrine therapy was 1.34 QALYs, with a lifetime cost of $154 961 (Table 2). PAL + FUL was estimated to provide higher quality-adjusted life expectancy (1.46 QALYs) at greater costs ($269 551), resulting in an incremental cost-effectiveness ratio of $918 166 per QALY gained. The incremental cost-effectiveness ratios were $455 243 per QALY at a 50% cost of PAL, $206 085 per QALY at a 25% cost of PAL, and $89 219 per QALY at a 10% cost of PAL (Table 2). At a willingness-to-pay threshold of $100 000 per QALY, the probabilities of PAL + FUL being the cost-effectiveness strategy compared with usual care (i.e. FUL) were 1%, 11%, and 67% at 50%, 25%, and 10% of the current cost of PAL, respectively (supplementary Figure S5, available at *Annals of Oncology* online). Without a substantial reduction in the cost of PAL, the usual care was the optimal treatment strategy for patients with prior endocrine therapy.

Discussion

Adding PAL to usual care results in significantly longer median PFS time and moderate increase in quality-adjusted life expectancy in postmenopausal women with ER-positive, HER2-negative advanced breast cancer. However, at the current prices, PAL appears unlikely to be cost-effective relative to the usual care from a societal perspective. In treatment-naive patients,

Table 2. Summary results of base-case and sensitivity analyses[a]

Treatment strategy	Cost, $	Effectiveness, QALYs	Incremental Cost, change in $	Incremental QALYs, change in QALYs	Incremental cost-effectiveness, change in $/change in QALYs
Patient who had not received any endocrine treatment					
LET	128 435 (103 519 to 198 755)	1.82 (1.31 to 3.05)	Reference	Reference	Reference
PAL+LET	372 761 (265 256 to 602 382)	2.13 (1.53 to 3.47)	244 326 (129 337 to 463 035)	0.32 (−0.74 to 1.45)	768 498 (−5 202 382 to 5 951 366)
PAL at 50% cost+LET	245 260 (183 839 to 374 048)	2.13 (1.53 to 3.47)	116 825 (47 637 to 232 833)	0.32 (−0.74 to 1.45)	367 459 (−2 262 634 to 2 707 466)
PAL at 25% cost+LET	177 714 (140 471 to 263 663)	2.13 (1.53 to 3.47)	49 280 (4 199 to 119 359)	0.32 (−0.74 to 1.45)	155 003 (−804 542 to 1 001 167)
PAL at 10% cost+LET	140 339 (112 993 to 202 715)	2.13 (1.53 to 3.47)	11 904 (−23 302 to 52 846)	0.32 (−0.74 to 1.45)	37 443 (−164 289 to 213 700)
Patient who had a prior endocrine therapy					
FUL	154 961 (122 932 to 232 860)	1.34 (0.95 to 2.49)	Reference	Reference	Reference
PAL+FUL	269 551 (217 900 to 368 220)	1.46 (1.13 to 2.19)	114 591 (57 454 to 186 844)	0.12 (−0.79 to 0.55)	918 166 (−5 004 221 to 5 712 608)
PAL at 50% cost+FUL	211 777 (174 577 to 291 640)	1.46 (1.13 to 2.19)	56 816 (13 954 to 101 178)	0.12 (−0.79 to 0.55)	455 243 (−2 386 396 to 2 750 636)
PAL at 25% cost+FUL	180 681 (151 218 to 254 975)	1.46 (1.13 to 2.19)	25 720 (−9660 to 59 980)	0.12 (−0.79 to 0.55)	206 085 (−1 080 510 to 1 238 756)
PAL at 10% cost+FUL	166 095 (136 861 to 235 651)	1.46 (1.13 to 2.19)	11 135 (−25 160 to 35 808)	0.12 (−0.79 to 0.55)	89 219 (−304 799 to 396 343)

[a]Values in parentheses represent 95% credible intervals derived from the results of probabilistic sensitivity analysis. LET, letrozole; PAL, palbociclib; FUL, fulvestrant.

PAL + LET cost $768 498 per additional QALY gained compared with LET. In patients with prior endocrine therapy, PAL + FUL cost $918 166 per additional QALY gained compared with FUL. Probabilistic sensitivity analysis suggested a small probability of PAL being cost-effectiveness compared with usual care at conventional willingness to pay thresholds (typically $50 000–$200 000 per QALY) [36], unless the cost of PAL was substantially reduced.

Our study is the first cost-effectiveness US-based analysis of PAL for the treatment of women with advanced breast cancer. Our results agree with those from an analysis by Matter-Walstra et al. [10] cunducted in Switzerland. They reported that PAL + LET compared with LET had a 0% chance of being cost-effective at a willingness-to-pay threshold of CHF 100 000 per QALY. Our study resulted in smaller incremental QALYs, mainly because we assumed that if PAL does not stop disease progression, patients cam still benefit from alternative treatment options such as chemotherapy. Previous studies that examined other recently approved molecular or monoclonal targeted therapies for the patients with metastatic breast cancer also concluded that adding those therapies to usual care were not considered cost-effective [19, 37, 38].

Although efficacy of adding PAL to LET has been demonstrated in terms of prolonging PFS in treatment-naive women with advanced breast cancer, its impact on patients' OS was modest (37.5 and 33.3 months, respectively) [7]. In many settings, no correlation is observed between PFS and OS as patients' life expectancy is modified by subsequent therapies, particularly in cases with long periods of survival following disease progression [39, 40]. Another important reason for unfavorable cost-effectiveness results is the high cost of PAL. While paclitaxel was the only commonly used cancer drug costing ∼$2500 per month up to 20 years ago, the majority of cancer drugs used today substantially exceed the price of paclitaxel without providing significant additional benefit in terms of life-years [41]. In the setting of metastatic disease, where patient life-years are limited, cost-effectiveness analyses rarely produce favorable results for these expensive cancer treatments.

Our model has several limitations. We assumed a specific type and sequence of therapies after PAL treatment, which were not reported in the PALOMA1 and PALOMA3 studies. In practice, the choice of subsequent therapy may be affected by the physician's preference or individual patient situations and can differ from our assumptions. Our model did not incorporate dose reductions in response to adverse events or patient adherence to treatment, which would alter the total cost and effectiveness of PAL. However, we believe this assumption has little impact in the conclusions of our study. In the absence of reliable price estimates for PAL, we decided to use wholesale acquisition costs of drugs in our base-case analysis, which do not reflect actual negotiated prices after potential discounts and rebates. However, we believe our sensitivity analysis provides useful information regarding the impact of drug price on cost-effectiveness results. Finally, we restricted our analysis to direct medical costs and also did not consider the cost of grade 1 or 2 adverse events.

From the societal and payer's perspective, the prices for many cancer drugs are not affordable. The present study is another example that demonstrated a remarkably effective cancer drug is not cost-effective unless the drug price was discounted by 90%.

Although many other factors should be taken into consideration in making treatment and coverage decisions, we believe that cost-effectiveness analysis results provide an important insight about the relative value of a new medication compared with alternative treatment options from the societal point of view. Recent efforts to incorporate value-based frameworks by non-profit organizations and medical societies [42] can use cost-effectiveness results to improve efficiency and outcomes of these healthcare organizations.

In conclusion, the results of the present study indicate that PAL treatment is unlikely to be cost-effective compared with the usual care from a societal perspective at the current prices. Given significant clinical effect that adding this drug to usual regimens can result, it warrants broader discussions and negotiations in regard to the pricing of this innovative drug.

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Disclosure

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