□原著論文□

Cost-effectiveness analysis of palbociclib as first-line treatment for patients with ER-positive, HER2-negative advanced breast cancer in Japan

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Abstract

Purpose: To evaluate the cost-effectiveness of palbociclib (PAL) plus letrozole (LET) compared with LET alone as first-line therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) unresectable or recurrent breast cancer.

Methods: We developed a Markov model to estimate the cost-effectiveness of PAL plus LET compared with LET alone over a 15-year period. Cost-effectiveness analysis was performed from the Japanese healthcare payer's perspective. Clinical outcomes were derived from the PALOMA-1 and PALOMA-2 studies. Quality-adjusted life year (QALY) and incremental cost-effectiveness ratio (ICER) were calculated. Direct medical costs and QALY were discounted at 2% per year. One-way sensitivity analyses were performed to estimate the uncertainty of the results.

Results: Incremental costs and QALY when PAL was added to LET therapy were 8,670,801 JPY and 0.388 QALY, respectively. ICER between PAL plus LET and LET alone was 22,345,821 JPY/QALY. ICER exceeded 7.5 million JPY/QALY, which was the willingness-to-pay threshold for anti-cancer drugs in Japan. According to one-way sensitivity analyses, PAL plus LET therapy was not cost-effective.

Conclusion: PAL plus LET was not cost-effective compared with LET alone for first-line treatment of advanced breast cancer in Japan.

Keywords：palbociclib, letrozole, cost-effectiveness, advanced breast cancer

Ⅰ. Introduction

Breast cancer has high prevalence in Japanese women with an annual incidence of approximately 95,000 in 2016 and annual number of deaths exceeding 14,000 in 2017. Among the cancer types, breast cancer is ranked 1st and 5th for incidence and number of deaths in women, respectively, in Japan[1)].

Advanced breast cancer is generally treated based on Hortobagyi's algorithm, and in cases where 'life-threatening metastasis is absent' and are hormone-sensitive positive, treatment starts with endocrine therapy. When the patient condition becomes life-threatening, treatment is changed to chemotherapy[2)]. Accordingly, treatment of estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative postmenopausal breast cancer is initiated with the administration of hormone therapy drugs, such as an aromatase inhibitor, as first-line treatment.

Palbociclib is a cyclin dependent kinases 4 and 6 (CDK4/6) inhibitor that stops tumor growth by arresting cell cycle. It was shown to be safe and effective in randomized phase II and III trials for ER-positive, HER2-negative advanced postmenopausal breast cancer[3–6)]. In an open-label randomized phase II study, the PALOMA-1 study, when ER-positive, HER2-negative advanced postmenopausal breast cancer patients were administered a combination of palbociclib and letrozole as first-line treatment, the median progression-free survival (PFS) was 20.2 months compared with 10.2 months for those who received letrozole alone (HR, 0.488; 95% CI, 0.319－0.748; one-sided p=0.0004) [3)]. In a global phase III study, the

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PALOMA-2 study, PFS was significantly extended by palbociclib plus letrozole therapy compared with those receiving placebo plus letrozole. Overall survival was not shown since the study had not reached the necessary number of events to perform the analysis[4]. Regarding the patient-reported outcomes in the PALOMA-2 study, no significant differences were observed between both groups in changes from baseline in FACT-Breast Total, FACT-General Total, or EQ-5D scores[5]. In the PALOMA-2 study, Japanese patients accounted for 6.9% (46/666) of the overall population. The efficacy was consistent with the overall population[6].

Based on the results of these clinical studies, palbociclib was approved for use in combination with endocrine therapy for women with unresectable or metastatic breast cancer in 2017 in Japan.

The 2018 Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer strongly recommended a combination of aromatase inhibitor and CDK4/6 inhibitor as first-line endocrine therapy for postmenopausal hormone receptor-positive advanced breast cancer[7]. There is no description in the guideline regarding cost-effectiveness analysis of palbociclib. Individualized medical care for advanced breast cancer has progressed due to the development of various targeted drugs, such as palbociclib. However, since most are costly, cost-effectiveness of the drug as well as its efficacy and safety should be considered.

Based on the pilot program of cost-effectiveness assessment of pharmaceuticals and medical devices in Japan in 2016, the health outcome was assessed based on the quality-adjusted life year (QALY) and the incremental cost-effectiveness ratio (ICER). Drug prices that were deemed as cost-intensive by the Ministry of Health, Labour and Welfare were slashed during a revision of drug prices in April 2018. In a cost-effectiveness assessment scheme introduced in April 2019, oncology drugs were specified with requiring special consideration, and the reference value used for price adjustment was set at 7.5 million JPY/QALY[8]. Studies regarding health technology assessment have been performed in other countries, and, of these, there are 4 that performed cost-effectiveness analyses of palbociclib[9–12]. All studies found that the addition of palbociclib to endocrine therapy was not cost-effective. However, it may be important to investigate cost-effectiveness under the Japanese healthcare system since medical expenses, such as drugs, are different between countries. Therefore, we conducted a cost-effectiveness analysis of palbociclib plus letrozole as first-line treatment for ER-positive, HER2-negative advanced breast cancer compared with that of letrozole alone using a Markov state transition model based on the results of the PALOMA-1 study.

Ⅱ. Materials and Methods

1. Model structure

We constructed a Markov model[13] to conduct this simulation analysis based on the PALOMA-1 study. The model used 3 mutually exclusive health states: progression-free (PF), progression, and death. The model simulated state transition in patients with breast cancer over a prolonged period (Figure 1). The results from ER-positive, HER2-negative advanced breast cancer postmenopausal patients in the PALOMA-1 study were applied to the Markov model. Patients began in the PF state and were randomly assigned palbociclib plus letrozole or letrozole as first-line treatment. Patients orally received 125 mg palbociclib per day in 4 week cycles (3 weeks of treatment followed by 1 week off) or placebo. All patients orally received 2.5 mg letrozole per day. Patients continued with the treatment until they experienced disease progression or developed toxic effects. Patients who experienced progression after first-line treatment were able to receive subsequent treatment. The outputs of the model are life-time cost, life year (LY), and QALY. A discount rate of 2% per year was applied to the costs and QALY according to the guideline[8]. The Markov model was developed in

Figure 1　Markov model.
Patients received palbociclib plus letrozole or letrozole alone in the progression-free state. Some patients who progressed after first-line therapy received second-line therapy.

Microsoft® Excel. A week per cycle and a time period of 15 years were used to obtain the required number of outcomes. Cost-effectiveness analysis was conducted from a Japanese healthcare payer's perspective.

2. Transition probabilities and model estimation results

Efficacy of the clinical outcome was derived from the PALOMA-1 study, and transition probabilities were assessed from this data. The PALOMA-1 study was conducted outside Japan. From the results of the PALOMA-1 study, the median OS was 37.5 and 33.3 months for patients who received palbociclib plus letrozole and letrozole alone, respectively, and the median PFS was 20.0 and 10.2 months for patients who received palbociclib plus letrozole and letrozole alone, respectively. PFS rates at 12 months were 71.8 and 41.7% in the palbociclib plus letrozole and letrozole alone groups, respectively, based on the Common Technical Document of the PALOMA-1 study. OS rates at 12, 24, and 36 months in the palbociclib plus letrozole group were 89.0%, 77.1%, 53.0%, respectively, and 87.0%, 70.2%, 44.0%, respectively, in the letrozole alone group.

3. Cost

We estimated the cost of each of the three states from an incremental approach based on a standard treatment process in Japan. To perform this analysis from the perspective of the Japanese public healthcare system, we calculated direct medical costs and estimated the cost of each health state in both treatment arms. We assessed data regarding medical costs from literature[14, 15] and calculated costs by referencing drug price and medical treatment fee lists as a fee-for-service system. The costs of both palbociclib and letrozole were calculated based on the results of the PALOMA-2 study. We deemed the administration period to be the same as mPFS and estimated drug costs per week considering the relative dose intensity in Japanese patients. A list of second-line therapies was derived from the results of the PALOMA-2 study[16]. Drug costs per week were calculated by estimating the period of each drug administration from different clinical trials and Post Progression Survival (PPS) based on the PALOMA-1 study. Third-line treatment was not included in the direct medical cost since it could not be calculated from the published data. Furthermore, management costs for adverse events greater than G3, such as neutropenia due to palbociclib, was not included in the direct medical cost in order to analyze cost by dose modification and interruption.

4. Utilities

We used a utility of 0.7245 and 0.4492 in the PF and progression state, respectively, in both drug groups based on the NICE data[17] that was used in previous studies[18]. EQ-5D scores were used from the PALOMA-2 study.

5. Assessment of cost-effectiveness

We evaluated the cost-effectiveness between palbociclib plus letrozole and letrozole alone based on ICER, which was calculated from the following equation:

ICER = (cost of combination therapy − cost of monotherapy) / (QALY of combination therapy − QALY of monotherapy).

Table 1　Transition probabilities.

	PF → PF	PF → P	PF → D	P → P	P → D	D → D
Palbociclib + Letrozole (0-52 week)	0.99365	0.00635	0	0.98020	0.01980	1
Palbociclib + Letrozole (53-104 week)	0.98750	0.01250	0	0.99260	0.00740	1
Palbociclib + Letrozole (105-780 week)	0.98750	0.01250	0	0.98760	0.01240	1
Letrozole (0-52 week)	0.98334	0.01666	0	0.99110	0.00890	1
Letrozole (53-104 week)	0.98334	0.01666	0	0.99365	0.00635	1
Letrozole (105-780 week)	0.98334	0.01666	0	0.98874	0.01126	1

PF, progression-free; P, progression; D, Death.
Value represent transition probabilities per week.

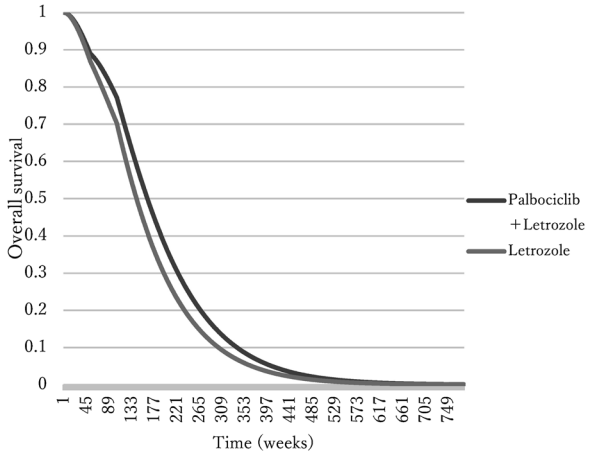

Figure 2-1　Overall survival model

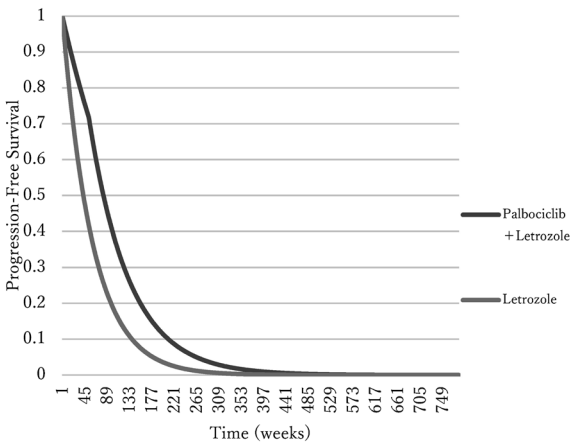

Figure 2-2　Progression-free survival model

Figure 2

Figures 2-1 and 2-2 are created based on the transition probabilities calculated from PALOMA-1.

ICER was considered to be cost-effective below 7.5 million JPY/QALY[8] and was also set as the threshold.

6. Sensitivity analysis

We carried out one-way sensitivity analyses to clarify overall uncertainty in the results. We evaluated potential parameters that had significant influence on the results based on the tornado diagram. A variation of ±20% was applied to several parameters of transition probabilities, drug cost of palbociclib, direct medical cost (excluding cost of palbociclib), and utilities. We set a broad variation of ± 20% since it was deemed sufficient by previous study[19]. Discount rates were also varied between 0 and 4% in accordance with the guideline[8].

7. Ethical approval

Ethical approval was not obtained because all the data of this study was derived from published information.

Ⅲ. Results

1. Transition probabilities and model estimation results

The transition probabilities calculated from the data of the PALOMA-1 study are shown in Table 1. Figure 2 shows OS and PFS over a period of 15 years using this model. It

Table 2　Base case analysis.

	Total costs (JPY)	Incremental costs (JPY)	QALY	Incremental QALY	ICER (JPY/QALY)
Palbociclib plus Letrozole	10,686,975	-	2.037	-	-
Placebo plus Letrozole	2,016,174	8,670,801	1.648	0.388	22,345,821

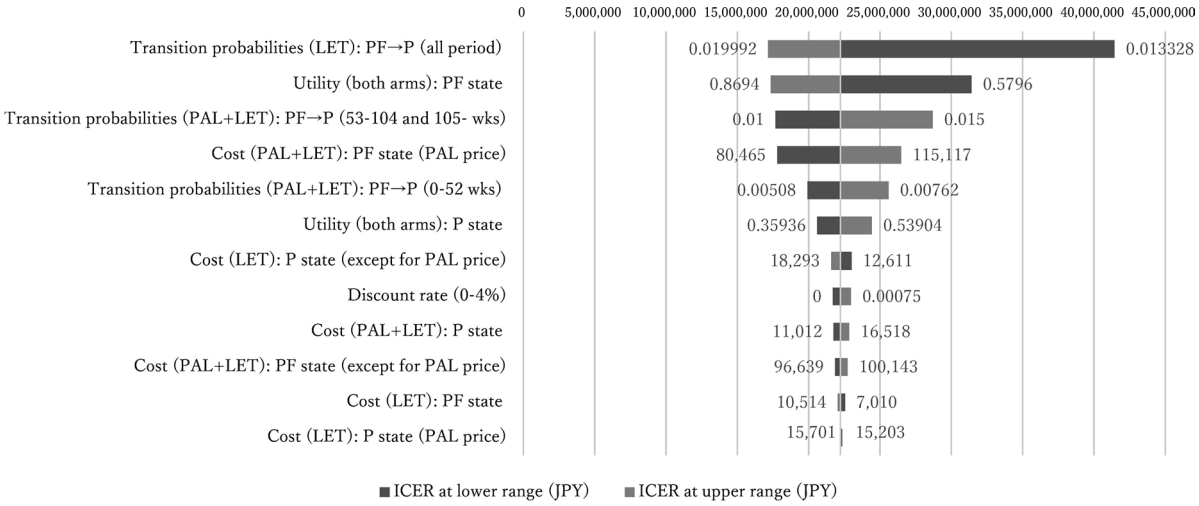

Figure 3　Tornado diagram (one-way sensitivity analysis).
PAL+LET, palbociclib plus letrozole; LET, letrozole; PF, progression-free; P, progression; ICER, incremental cost-efffectiveness ratio.

seems that OS and PFS of our model are similar to the results from PALOMA-1 study.

2. Costs

In addition to calculating the costs for resources under a fee-for-service system, we estimated the direct medical costs of the three health states based on the therapies required to treat breast cancer proposed by previous studies[14,15]. As a result, the costs per week for receiving combination therapy and monotherapy in the PF state were 98,391 and 8,762 JPY, respectively. The costs per week for receiving combination therapy and monotherapy in the progression state were 13,765 and 15,452 JPY, respectively.

3. Assessment of cost-effectiveness

The results of the cost-utility analysis and cost-effectiveness are shown in Table 2. Expected costs for palbociclib plus letrozole and letrozole alone were 10,686,975 and 2,016,174 JPY, respectively. Gained QALY for palbociclib plus letrozole and letrozole alone were 2.037 and 1.648 QALY, respectively. The cost of adding palbociclib to letrozole alone treatment was 8,670,801 JPY, and the incremental gained QALY was 0.388 QALY. The ICER for palbociclib plus letrozole, compared with letrozole alone, was 22,345,821 JPY per QALY.

4. Sensitivity analysis

The results of one-way sensitivity analysis are shown in Figure 3. The parameter that most affected the results was transition probability from PF to progression state in letrozole alone therapy. Across a wide range for each parameter, the ICER remained > 7.5 million JPY per QALY. Therefore, our results were robust.

Ⅳ. Discussion

The objective for advanced breast cancer treatment is to extend survival; however, it is important to clarify whether the cost of treatment is reasonable since recent molecular-

targeting drugs are expensive and result in large medical expenses.

To our knowledge, this is the first study to perform a cost-effectiveness analysis of palbociclib that reflects the medical environment in Japan. In this study, the outcomes of unresectable or recurrent breast cancer patients treated with palbociclib plus letrozole or letrozole alone were simulated using the Markov model, and a cost-utility analysis was performed. In a simulation spanning over 15 years, the total cost of palbociclib plus letrozole treatment increased by 0.388 QALY and was approximately 8.6 million JPY compared with that of letrozole alone. However, palbociclib plus letrozole treatment may be superior to letrozole alone when QOL is considered. The ICER for palbociclib plus letrozole, compared with letrozole alone, was approximately 22 million JPY/QALY. In other countries, willingness-to-pay (WTP), the maximum medical cost patients are willing to pay, is set as the ICER, which is as an assessment criterion of cost-effectiveness. Cost-effectiveness is considered favorable when ICER is less than 20,000-30,000 pounds/QALY in England[17]. In Japan, there is no clear consensus; however, 5−6 million JPY per QALY is considered acceptable[20]. Since anti-cancer drugs are considered as items requiring consideration, the cost of 7.5 million JPY/QALY was used as the reference value for price adjustment corresponding to the ICER set by the Central Social Insurance Medical Council. In this study, we considered cost-effectiveness as favorable when ICER was less than 7.5 million JPY/QALY. Accordingly, it was suggested that the cost-effectiveness of palbociclib plus letrozole therapy is not superior to that of letrozole alone in Japan. When each parameter was changed to within a range of ±20% by one-way sensitivity analysis, ICER was not lower than 7.5 million JPY/QALY for any parameter. The most influential parameter was transition probability from PF to progression state in letrozole alone treatment.

Similar studies of our research have been published in Switzerland, the US, and Canada. The Markov model was used in the analysis performed in Switzerland; however, discrete event simulation model was used in the US and Canada. In addition to the models, the utility and medical expenses, such as drug cost, used in the analysis of some countries were different. Furthermore, the cost-effectiveness assessment and robustness in the sensitivity analysis in some studies were insufficient. In this study, similar to the results of the other countries, the palbociclib plus letrozole therapy was not favorable in terms of cost-effectiveness. In our analysis, transition probability was calculated based on the clinical parameters of the PALOMA-1 study; however, registered patient background varied among clinical studies and a broad range of patients were treated. For example, in a pre-specified subgroup analysis, the treatment effect was generally consistent regardless of the patient having visceral disease or not[21]. When administering palbociclib with endocrine therapy as first-line treatment, other medical conditions of the patients should also be considered. The PALOMA-3 study included patients receiving palbociclib plus fulvestrant or placebo plus fulvestrant as second or greater lines. In the PALOMA-3 study, the differences in overall survival were not significant, however, combination treatment resulted in longer overall survival[22], and their EQ-5D index score was also high[23]. Based on these results, further studies regarding the cost-effectiveness of palbociclib in second-line and further treatment are required. Although cost may not necessarily influence treatment strategy, it would be helpful for physicians in deciding an appropriate treatment process. We suggest that information on cost-effectiveness analysis could be included in the guidelines.

There are several limitations in this study. First, regarding the clinical parameters used in the Markov model, the transition probability was calculated based on the clinical outcomes of a phase II study, the PALOMA-1 study. We would have used the results of Japanese patients in the confirmatory phase III study, PALOMA-2 study; however,

the data regarding overall survival was incomplete. In addition, NICE data was used for the utility value; however, QOL values for Japanese patients would have been preferred. Even though the PALOMA-2 study included Japanese patients, the results of the overall population are required. When clarifying cost-effectiveness, previous studies cited utility values from a clinical study other than the PALOMA-2 study, which suggests that our study regarding cost-utility analysis using the utility value with palbociclib is valuable.

Secondly, the mortality of the general population, including deaths from causes other than breast cancer, was not considered in this model. The validity of the model was clarified by comparing the mortality of the patients in this model with an abridged life table (fundamental statistics) from the Ministry of Health, Labor and Welfare. The median age of patients registered in the PALOMA-1 study was 63 and 64 years in the palbociclib plus letrozole and letrozole alone groups, respectively. Since the analytical period of this model was 15 years, the mortality was compared between those aged 78−79 years in this model and 79 years in the 2018 abridged life table (female), and the mortalities were 0.44040% and 0.01953%, respectively. The breast cancer mortality in this model was considerably higher than that of the general population, suggesting that there may be discrepancies when the mortality data of the general population are not used.

The third limitation is due to the estimation of medical expenses. The guidelines from the second edition of analysis of cost-effectiveness assessment by the Central Social Insurance Medical Council recommend the use of the claims database in Japan, which reflect the standard medical care process in Japan, for cost estimation. Since the claims database could not be used in this study, it was calculated by the incremental method based on previous studies. The drug cost of second-line treatment was calculated based on the rate of drugs used in the PALOMA-2 study; however, since the data regarding the administration period of each drug in the PALOMA-2 study was not published, it was separately cited from different clinical studies. Therefore, it was calculated based on the data of groups with different patient backgrounds. However, considering the rate of transition to second-line treatment and the cost of each drug, the cost of second-line treatment may be small compared with that of palbociclib, suggesting that it is not a significant factor. Similarly, since post-progression survival in second-line treatment could not be calculated, analysis was performed without considering drugs used for third-line or later treatments; however, there may have been a minor influence on total cost when the rate of transition to third-line treatment and administration period are considered. In addition, the cost for adverse events was not included in this research. Adverse events due to palbociclib, such as neutropenia, may occur but is managed by drug interruption or dose modification. In the Japanese population, G-CSF administration was required to treat febrile neutropenia in 2 of 101 patients included in the analysis in the phase II, PALOMA-2, and PALOMA-3 studies. Clarification of the cost for adverse events and further studies clarifying a model incorporating these costs are required.

The fourth limitation is due to the sensitivity analysis. We performed one-way sensitivity analysis; however, conducting probabilistic sensitivity analysis in addition to one-way sensitivity analysis is preferred according to the guidelines for analysis of the cost-effectiveness assessment by the Central Social Insurance Medical Council.

Despite the limitations to this study, the results of the ICER estimation and cost-effectiveness are unlikely to change since the estimated ICER was larger than the threshold of 7.5 million JPY/QALY based on the sensitivity analysis.

Ⅴ. Conclusion

Palbociclib plus letrozole for first-line treatment of ER-positive, HER2-negative unresectable or recurrent breast

cancer increased QALY. However, from the cost utility analysis, ICER exceeded 7.5 million JPY/QALY. Therefore, palbociclib plus letrozole therapy is unlikely to be cost-effective compared with letrozole monotherapy in Japan.

Competing interests

T.M is an employee at Novartis Pharma K.K. and belongs to the oncology medical affairs department. No sponsors were involved in this research.

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手術不能又は再発乳がんに対する一次治療としてのパルボシクリブの費用対効果に関する研究

森本　喬士　　池田　俊也　　山崎　力

抄　録

はじめに：ホルモン受容体陽性，HER2 陰性の手術不能又は再発乳がんに対する一次治療としてのパルボシクリブ（PAL）+ レトロゾール（LET）療法の LET 単独療法に対する費用対効果を評価した．
方法：マルコフモデルを構築し 15 年にわたるシミュレーションをした．公的医療の立場から分析し，直接医療費を算出し評価した．効果指標は質調整生存年（QALY）を用いた．費用対効果は増分費用効果比（ICER）を用いて評価し，費用と QALY は年率 2% で現在価値に割り引いた．結果の頑健性は一元感度分析で評価した．
結果：LET に対する PAL の上乗せによる増分費用は 8,670,801 円であった．増分 QALY は 0.388QALY であった．単独療法を基準とした場合の併用療法の ICER は 22,345,821 円 /QALY であり，本邦において抗がん剤による費用対効果が優れるとされる上限値 750 万円 /QALY を上回った．一元感度分析によっても結果の頑健性が示唆された．
考察：PAL ＋ LET 療法は，LET 単独療法と比較して費用対効果に優れる治療とはいえなかった．

キーワード：パルボシクリブ，レトロゾール，費用効用分析，手術不能又は再発乳がん