Department of Pharmacy, Ogaki Municipal Hospital, Gifu, Japan

Cost-effectiveness and safety of palbociclib and everolimus for treating advanced and recurrent breast cancer

M. Kimura*, E. Usami, T. Yoshimura

Received August 6, 2019, accepted September 10, 2019

**Corresponding author: Michio Kimura, Department of Pharmacy, Ogaki Municipal Hospital, 4-86 Minaminokawa-cho, Ogaki-shi, Gifu 503-8502, Japan kimkim0305nao@yahoo.co.jp*

Pharmazie 74: 763-766 (2019) *doi:10.1691/ph.2019.9719*

This retrospective study compares the economic superiority of palbociclib *versus* everolimus for advanced and recurrent breast cancer. Furthermore, we investigated the safety and treatment continuity of palbociclib and everolimus regimens. Expected costs were calculated based on data from patients with advanced and recurrent breast cancer who were treated with palbociclib and everolimus. The progression-free survival (PFS) from the PALOMA-3 clinical trial and BOLERO-2 clinical trial was used to evaluate the therapeutic efficacy of the regimens. The cost-effectiveness ratio of each chemotherapy agent was calculated by dividing the expected cost by the progression-free survival (PFS). The cost-effectiveness ratio per month was JPY 391,551.3/PFS for palbociclib and JPY 488,690.5/PFS for everolimus (p=0.627). The incremental cost-effectiveness ratio per month of everolimus to palbociclib was JPY 100,133.7/PFS. For patients receiving everolimus, adverse drug reactions included stomatitis (77.3%), rash (59.1%) and leukopenia (59.1%). For patients receiving palbociclib, neutropenia (69.2%), leukopenia (69.2%) and anemia (30.8%) occurred. In terms of discontinuation owing to adverse events (AEs), pneumonitis, thrombocytopenia, edema, fatigue, and neutropenia were experienced in the everolimus group. The cost-effectiveness of everolimus and palbociclib are equivalent, but since the prevalence of AEs is high in patients receiving everolimus, its AE management is important.

1. Introduction

A treatment for metastatic and recurrent breast cancer should be selected that will prolong survival while maintaining quality of life (QOL) according to the individuality and hope of each patient instead of simply aiming to cure, as is the case for initial breast cancer (Motoo 2016). In advanced hormone receptor-positive, human epidermal growth factor receptor type 2 (HER2)-negative breast cancer cases, cyclin-dependent kinase (CDK) 4/6 (palbociclib) and mTOR (everolimus) inhibitors, which target molecules involved in cancer progression, prolong progression-free survival (PFS) when administered in combination with hormonal drugs versus administration of a hormone blockade alone (Finn et al. 2016; Turner et al. 2015; Baselga et al. 2012). The American Society of Clinical Oncology guidelines recommend CDK4/6 inhibitors as first-line and second-line treatments for ER-positive, HER2-negative advanced cancer (Rugo et al. 2016). The NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend endocardine therapy (±a CDK4/6 or mTOR inhibitor) as the standard for systematic treatment of recurrent or stage IV disease, including ER- and/or PR-positive, HER2-negative breast cancer. Thus, it is conceivable to use palbociclib (CDK4/6 inhibitor) or everolimus (mTOR inhibitor) for the treatment of advanced and recurrent breast cancer in various countries.

The high medical cost of these treatments is an important factor (Rugo et al. 2016), because long-term use of molecular-targeted drugs is expensive. The concept of drug economics must be used to reduce medical expenses, but this approach is more popular in Western countries than in Japan. As represented by the guidelines of the National Institute for Health and Clinical Excellence and the Canadian Agency for Drugs and Technologies in Health, an

Table 1: Patient characteristics

	Everolimus	Palbociclib	p value
Number	22	13	
Age, years			
Median (range)	63 (49-83)	60 (47-84)	0.767[a)]
Gender, n			
Male/female	0/22	0/13	0.861[b)]
Previous treatment line	5 (2-12)	5 (2-9)	0.473[a)]
Body surface area, m^2			
Median (range)	1.51 (1.44-1.65)	1.50 (1.20-1.73)	0.986[a)]
CrCl, mL/min	84.9 (52.9-136.5)	84.9 (34.8-127.5)	0.946[a)]
Disease status			
Unresectable	1	2	0.268[b)]
Recurrent	21	11	
Metastatic site			
Liver	8	5	0.964[b)]
Lung	9	7	
Peritoneal	1	1	
Lymph node	14	6	
Bone	18	8	
Brain	2	1	
Others	1	1	

a) Mann-Whitney's U test
b) Chi-square for independence test

economic evaluation has been mandated in the United States and European countries (Williams et al. 2008). However, no report is available on the cost-effectiveness and safety of palbociclib and everolimus for metastatic and recurrent breast cancer. Clarification of the cost-effectiveness and treatment continuation of these drugs will demonstrate their medical economic advantages and safety and help support decision making and treatment continuation when selecting treatment.

In this study, we evaluated the economic superiority of palbociclib *versus* everolimus for advanced and recurrent breast cancer. In addition, we examined the safety of palbociclib in Japan due to the limited number of reports available. Lastly, we investigated the safety and treatment continuity of palbociclib and everolimus regimens.

2. Investigations and results

2.1. Patient characteristics

The patient characteristics are summarized in Table 1. The median ages of the patients who received everolimus and palbociclib were 63 (range: 49–83) and 60 (range: 47–84) years, respectively, and the previous treatment lines were 5 lines (range: 2-12 lines) and 5 lines (range: 2-9 lines), respectively.

2.2. Cost data

For everolimus, the calculated direct medical costs per regimen included the medication fee (anticancer drugs = JPY 452,474.5 and supportive care drugs = JPY 17,307.5), inspection fee of JPY 8,775.5, and outpatient medical examination fee of JPY 2,466.8. For palbociclib, the calculated direct medical costs per regimen included the medication fee (anticancer drugs = JPY 504,924.6 and supportive care drugs = JPY 11,865.6), inspection fee of JPY 14,413.6, and outpatient fee of JPY 2,068.3. The total costs per course (28 days) of each regimen were JPY 487724.0 and JPY 538338.8, respectively (p = 0.927) (Table 2).

2.3. Cost-effectiveness analysis

The cost-effectiveness ratio per month was JPY 488,690.5/PFS for everolimus and JPY 391,551.3/PFS for palbociclib. No significant differences were found between the two regimens (Table 3; p = 0.627), and the ICER per month of everolimus to palbociclib was JPY 100,133.7/PFS.

Table 2: Details of cost data

Variable	Everolimus	Palbociclib	p value
Medication fee			
Anticancer drugs	452,474.5	504,924.6	0.956[a)]
Supportive care drugs	17,307.5	11,865.6	0.387[a)]
Inspection fee	8,775.5	14,413.6	0.672[a)]
Outpatient medical examination fee	2,466.8	2,068.3	0.053[a)]
Others	6,699.8	5,066.7	0.204[a)]
Total	487,724.0	538,338.8	0.927[a)]

Note: The amount shown in Table 2 represents the cost per course (28 days) of each regimen. Others includes drug information providing fee, outpatient prescription fee, dispensing technology basic fee, oncology patient service fee 3, etc. Unit: Japanese yen (JPY).
a) Mann-Whitney's U test

Table 3: Cost-effectiveness ratio

	Expected cost (JPY/person)	Cost-effectiveness ratio (JPY/PFS)	PFS
Everolimus	3,371,964.4	488,690.5	6.9
Palbociclib	3,602,271.8	391,551.3	9.2
p value	0.011[a)]*	0.627[a)]	NA

Note: PFS = progression-free survival; cost-effectiveness ratio = expected cost (JPY/person)/effectiveness (PFS).; NA, not applicable; a) Mann-Whitney's U test * $p < 0.05$

2.4. Adverse events analysis

The major adverse events (AEs) are summarized in Table 4. For patients receiving everolimus, these AEs consisted of stomatitis (77.3%), rash (59.1%), leukopenia (59.1%), and an increase in aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) (59.1%). For patients receiving palbociclib, neutropenia (69.2%), leukopenia (69.2%), anemia (30.8%), fatigue (23.1%), nausea (23.1%), and arthralgia (23.1%) occurred.

2.5. Treatment period and reasons for discontinuation

The treatment enforcement periods for the different regimens were as follows: everolimus, 278 (range: 13-603) days and palbociclib, 287 (range: 13-603) days; no differences were noted between the two groups. The reasons for discontinuation of everolimus included AEs in 5 patients, deterioration in performance status in 1 patient, and progressive disease (PD) in 13 patients. Eight patients discontinued palbociclib for PD. In terms of discontinuation due to adverse events, pneumonitis, thrombocytopenia, edema, fatigue, and neutropenia were experienced in the everolimus group (Table 5).

3. Discussion

In this study, we conducted an economic and safety analysis to compare the palbociclib and everolimus chemotherapeutic regimens for advanced and recurrent breast cancer. We found that palbociclib and everolimus had the same cost-effectiveness. For implementation of the palbociclib and everolimus regimens, anticancer drug expenses accounted for the majority of the total expenditure. However, the cost data in this study are based on the patient population of a single facility, and therefore cost data should be collected from several facilities in the future to allow the data to be applied more widely. According to surveys conducted by Shiroiwa Shiroiwa et al. (2010) and Ohkusa et al. (2016), a chemotherapeutic regimen is considered cost-effective if it costs less than 500-600 million yen per quality-adjusted life year (QALY). Because this study did not consider the patients' quality of life (QOL), accurate determination of the cost-effectiveness was impossible. However, because the incremental cost-effectiveness ratio (ICER) of palbociclib over everolimus was JPY 100,133.7/PFS, we believe that these regimens may be within the range considered good in terms of cost-effectiveness.

Regarding the development of AEs, patients receiving everolimus frequently developed non-hematological toxicity, such as stomatitis and diarrhea. Furthermore, various hematological and non-hematological AEs occurred in the everolimus-treated patients. In the palbociclib-treated patients, neutropenia was the most prevalent AE, and the incidence of non-hematological toxicity was lower than that of everolimus treatment. The AEs observed in this study were similar to those in the PALOMA-3 clinical trial (Turner et al. 2015) and the BOLERO-2 clinical trial (Baselga et al. 2012). Non-hematologic toxicities, such as fatigue, nausea, stomatitis, and rash, have been reported to lower a patient's QOL and increase withdrawal from treatment (Tsunoda et al. 2010; Ganguli et al. 2013). Therefore, the AEs experienced by the everolimus-treated patients may have greatly reduced their QOL. Discontinuation due to AEs occurred in 5/22 everolimus-treated patients (23%) but in no palbociclib-treated patients. This result suggests that non-hematologic toxicities affect treatment continuity in patients treated with everolimus. Therefore, AE management must be considered for everolimus treatment.

The severity of AEs can be reduced by pharmacist outpatient intervention. Todo et al. (2018) reported that comprehensive pharmaceutical care was highly effective for enhancing treatment outcomes by maintaining a patient's QOL. For instance, implementation of comprehensive pharmaceutical care remarkably reduces the incidence of severe oral mucositis. Additionally, Kimura et

Table 4: Adverse events

Everolimus							Palbociclib						
	Grade							Grade					
n = 22	1	2	3	4	All grades (%)		n = 13	1	2	3	4	All grades (%)	
Leucopenia	4	8	2	0	13	(59.1)	Leucopenia	1	3	5	0	9	(69.2)
Neutropenia	6	3	2	0	11	(50.0)	Neutropenia	0	4	4	1	9	(69.2)
Thrombocytopenia	5	3	0	0	8	(36.4)	Thrombocytopenia	1	0	0	0	1	(7.7)
Anemia	5	6	0	0	11	(50.0)	Anemia	3	1	0	0	4	(30.8)
AST/ALT increase	11	2	0	0	13	(59.1)	AST/ALT increase	1	0	0	0	1	(7.7)
Creatinine increase	2	0	0	0	2	(9.1)	Creatinine increase	0	0	0	0	0	(0.0)
Fatigue	10	1	0	-	11	(50.0)	Fatigue	3	0	0	-	3	(23.1)
Anorexia	1	0	0	0	1	(4.5)	Anorexia	0	0	0	0	0	(0.0)
Nausea	7	1	0	0	8	(36.4)	Nausea	3	0	0	0	3	(23.1)
Vomiting	6	0	0	0	6	(27.3)	Vomiting	0	0	0	0	0	(0.0)
Stomatitis	13	3	1	0	17	(77.3)	Stomatitis	1	0	0	0	1	(7.7)
Diarrhea	5	2	0	0	7	(31.8)	Diarrhea	1	0	0	0	1	(7.7)
Constipation	0	0	0	0	0	(0.0)	Constipation	2	0	0	0	2	(15.4)
Dysgensia	6	0	0	0	6	(27.3)	Dysgensia	0	0	0	0	0	(0.0)
Edema	9	1	0	-	10	(45.5)	Edema	0	0	0	-	0	(0.0)
Pruritus	11	1	0	-	12	(54.5)	Pruritus	1	0	0	-	1	(7.7)
Rash	12	1	0	0	13	(59.1)	Rash	1	0	0	0	1	(7.7)
Pneumonitis	7	0	0	0	7	(31.8)	Pneumonitis	0	0	0	0	0	(0.0)
Epistaxis	2	0	0	0	2	(9.1)	Epistaxis	0	0	0	0	0	(0.0)
Hypokalemia	11	0	0	0	11	(50.0)	Hypokalemia	0	0	0	0	0	(0.0)
Nail ridging	4	-	-	-	4	(18.2)	Nail ridging	1	-	-	-	1	(7.7)
Arthraigia	4	0	0	0	4	(18.2)	Arthraigia	3	0	0	0	3	(23.1)
Cholesterol high	6	5	4	6	21	(95.5)	Cholesterol high	0	2	0	0	2	(15.4)
Hyperglycemia	8	1	1	0	10	(45.5)	Hyperglycemia	0	0	0	0	0	(0.0)
Others	7	0	0	0	7	(31.8)	Others	1	0	0	0	1	(7.7)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 5: Reasons for discontinuation

	Everolimus, n=22	Palbociclib, n=13	p value
Reasons for discontinuation			
Adverse events	5	0	0.039
Decrease in PS	1	0	0.435
Deterioration in disease condition	2	0	0.263
PD	13	8	0.886
Other	1	0	0.435
Ongoing	0	5	

PS, performance status; PD, progressive disease
AEs include pneumonitis (2), thrombocytopenia (1), thrombocytopenia, edema and fatigue (1), neutropenia (1).

al. (2017) reported that treatment discontinuation due to AEs was prevented by conducting pharmacist outpatient interventions based on a pharmacological indicator, and the completion rate of postoperative chemotherapy with S-1 was improved.

The ICER calculated in this study is a relative evaluation and there is a problem that there is no threshold. Therefore, it is necessary to conduct an absolute evaluation using QALY in the future.

A limitation of this study is that it is a retrospective survey performed in a single hospital. Therefore, since the results of this research are data from a specific area, a nationwide survey, such as a multi-facility joint study, should be conducted in the future to increase the number of cases.

This study is the first to analyze the cost-effectiveness and safety of two types of chemotherapy regimens for advanced and recurrent breast cancer. The cost-effectiveness of everolimus is equivalent to that of palbociclib. However, since the prevalence of AEs is high in patients receiving everolimus, AE management is important for this regimen.

4. Experimental

4.1. Patients

Between June 2014 and August 2018, patients with advanced and recurrent breast cancer who were treated with palbociclib and everolims at Ogaki Municipal Hospital, Japan, were included in the study. Palbociclib was administered in combination with endocrine therapy, usually in adults, at a dose of 125 mg once daily after meals for 3 weeks, and then the drug was withdrawn for 1 week. This regimen was repeated for one cycle (28 days). Everolimus 10 mg was orally administered daily after meals.

4.2. Cost-effectiveness analysis

Patients received two or more courses of either palbociclib (n = 13) or everolimus (n = 22) for treatment of advanced and recurrent breast cancer. Either palbociclib or everolimus was administered after previous 5 lines treatment, were those data of efficacy or safety resulted from the sequential treatment but not only caused from palbociclib or everolimus, respectively.

Cost data: Cost data included direct costs incurred at the time of chemotherapy. Fees were collected for medication (including supportive care), inspection, and outpatient medical examinations. We collected information about drug prices from the Insurance Drug Encyclopedia (Pharmaceutical Society 2012) and medical fees from the Medical Fee Points Table (Kawakami 2008) to calculate the total medical expenses. The average medical cost per course was calculated using actual patient data. We also simulated the cost up to progression-free survival (PFS).

Calculation exclusions: The diagnostic imaging (chest computed tomography (CT)) costs and the labor costs of the medical staff were included for each chemotherapy treatment. We excluded these costs from the calculations in this analysis. We also excluded the facility running and depreciation costs, because they were difficult to calculate per patient.

Data source for therapeutic effect analysis: To evaluate the therapeutic effects of palbociclib and everolimus, PFS data from the PALOMA-3 clinical trial (Turner et al. 2015) and the BOLERO-2 clinical trial (Baselga et al. 2012) were used as the data source.

Cost-effectiveness: The cost-effectiveness analysis was conducted by determining the cost and efficacy data for each chemotherapy agent; these data were obtained using the methods described above. The cost-effectiveness ratio of each chemotherapy agent was calculated by dividing the expected cost by PFS. In addition, the incremental cost-effectiveness ratio (ICER) was used to examine the superiority of the palbociclib regimen over the everolimus regimen using the following equation:
ICER (JPY/PFS) = (expected cost of palbociclib – expected cost of everolimus) / (PFS with palbociclib – PFS with everolimus).

4.3. Adverse events analysis

Adverse events (AEs) were retrospectively investigated for each patient. The date of each AE was identified using electronic charts and pharmacy service records. The AE severity was classified according to the Common Terminology Criteria for Adverse Events (US Department Of Health And Human Services 2009).

4.4. Treatment period and reasons for discontinuation

The reasons for discontinuation of treatment and the treatment duration for patients who underwent each regimen were investigated retrospectively.

4.5. Statistical analysis

The Mann-Whitney U test was used to analyze the patients' characteristics and the cost-effectiveness. Significance was set at $p < 0.05$, and all statistical analyses were performed in EZR (v1.30, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda 2013).

4.6. Ethical considerations

Personal information was protected in the aggregated data. The present study was approved by the Institutional Review Board of Ogaki Municipal Hospital (no. 20190627-6). The requirement for informed consent was waived by the Institutional Review Board.

Conflicts of interest: None declared.

References

Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. New Engl J Med 366: 520–529.

Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ (2016) Palbociclib and letrozole in Advanced Breast Cancer. N Engl J Med 375: 1925–1936.

Ganguli A, Wiegand P. Gao X, Carter JA, Botteman MF, Ray S (2013) The impact of secondline agents on patients' health-related quality of life in the treatment for non-small cell lung cancer: a systematic review. Qual Life Res 22: 1015–1026.

Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48: 452–458.

Kawakami Y (2008) Medical fee points table. 35th edition. Social Insurance Institute, Tokyo.

Kimura M, Go M, Iwai M, Usami E, Teramachi H, Yoshimura T (2017) Usefulness of a pharmacist outpatient service for S-1 adjuvant chemotherapy in patients with gastric cancer. Mol Clin Oncol 7: 486–492.

Meropol NJ, Schrag D, Smith TJ, Mulvey TM, Langdon RM Jr, Blum D, Ubel PA, Schnipper LE; American Society of Clinical Oncology (2009) American Society of Clinical Oncology guidance statement: the cost of cancer care. J Clin Oncol 27: 3868–3874.

Motoo Y (2016) How long should cancer chemotherapy be continued? – From the viewpoint of duration of efficacy of molecular targeting drugs. Gan To Kagaku Ryoho 43: 819–823.

Ohkusa Y, Sugawara T (2016) Research for willingness to pay for one QALY gain. Iryo To Shaka 16: 157–165.

Pharmaceutical Society (2012) Insurance drug encyclopedia, Jiho, Tokyo.

Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, Fallowfield L, Fowble B, Ingle JN, Jahanzeb M, Johnston SR, Korde LA, Khatcheressian JL, Mehta RS, Muss HB, Burstein HJ (2016) Endocrine Therapy for Hormone Receptor-positive metastatic breast cancer: American Societyof Clinical Oncology Guideline. J Clin Oncol 34:3069-3103.

Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K (2010) International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Eco. 4: 422–437.

Todo M, Ueda S, Osaki S, Sugitani I, Takahashi T, Takahashi M, Makabe H, Saeki T, Itoh Y (2018) Improvement of treatment outcomes after implementation of comprehensive pharmaceutical care in breast cancer patients receiving everolimus and exemestane. Pharmazie 73: 110–114.

Tsunoda A, Nakao K. Tsunoda Y, Watanabe M, Matsui N (2010) Health-related quality of life of colorectal cancer patients receiving oral UFT plus leucovorin compared with those with surgery alone. Int J Clin Oncol 15: 153–160.

Turner NC, Huang Bartlett C, Cristofanilli M (2015) Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 373: 1672–1673.

US Department Of Health And Human Services (2009) Common terminology criteria for adverse events (CTCAE) version 4.0. United States, National Cancer Institute. (http://www. acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009–09–15_QuickReferenc e_5X7.pdf).

Williams I, McIver S, Moore D, Bryan S (2008) The use of economic evaluations in NHS decision-making: a review and empirical investigation. Health Technol Assess 12: 1–175.