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Improvement of treatment outcomes after implementation of comprehensive pharmaceutical care in breast cancer patients receiving everolimus and exemestane

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Combination therapy with everolimus and an aromatase inhibitor such as exemestane is an effective treatment option for advanced or recurrent breast cancer. However, the therapy is often limited because of the occurrence of severe adverse events (AEs), including oral mucositis, interstitial lung disease, diarrhea, and rash. Therefore, early management of AEs is extremely important to obtain maximum treatment outcome. We investigated here the effects of comprehensive pharmaceutical care for prevention of severe AEs on patient's quality-of-life (QOL) and continuation of therapy. QOL was assessed every month based on the five-level version of EuroQol-5-Dimension (EQ-5D-5L). AEs were graded according to the Common Terminology Criteria for Adverse Events (ver 4.0). Implementation of comprehensive pharmaceutical care remarkably reduced the incidence of severe oral mucositis as compared with those without such interventions. EQ-5D-5L health states were almost constant during 6 months after intervention, ranging from 0.850 to 0.889. Median time to treatment failure (TTF) was significantly longer after intervention than before [224.0 days, 95% confidence interval (CI): 117–331 days *versus* 34 days, 21–47 days, hazard ratio (HR): 0.027, 95% CI: 0.005 – 0.154, p<0.001]. These findings suggest that our comprehensive pharmaceutical care is highly effective for enhancing treatment outcome by maintaining patient's QOL.

1. Introduction

Approximately 80% of breast cancer patients in Japan are hormone receptor (HR)-positive for estrogen receptors (ERs) or progesterone receptors (PgRs), thus endocrine inhibition is the cornerstone of the therapy for HR-positive breast cancer (National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (2014). Breast Cancer: Version 1.). In postmenopausal breast cancer patients, aromatase inhibitors such as exemestane are shown to be superior to ER modulators, including tamoxifen, in tumor response, prolongation of progression-free survival or overall survival (Mouridsen et al. 2003; Paridaens et al. 2008). However, continuous use of aromatase inhibitors or ER modulators may ultimately lead to the development of resistance to endocrine therapy (Ariazi et al. 2006). It has been demonstrated that upregulation of phosphatidylinositol-3 kinase/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway is implicated in the resistance to anti-hormone therapy (Beeram et al. 2007; Miller et al. 2010). Therefore, mTOR is considered to become a new target molecule in the therapy of HR-positive breast cancer patients showing resistance to the endocrine therapy (Crowder et al. 2009; Miller et al. 2010). Oral administration of everolimus, a specific mTOR inhibitor (Beuvink et al. 2005), in combination with exemestane, has been shown to be highly effective for improving progression-free survival in postmenopausal HR-positive advanced breast cancer (Baselga et al. 2012; Yardley et al. 2013; Noguchi et al. 2014; Ito et al. 2015). However, everolimus causes a number of severe adverse events (AEs) such as oral mucositis, interstitial lung disease, diarrhea, and rash (Baselga et al. 2012; de Oliveira et al. 2011; Efeyan and Sabatini 2010; Ito et al. 2015; Noguchi et al. 2014; Pritchard et al. 2013; Rugo et al. 2014; Yardley et al. 2013). In particular, oral mucositis is one of dose-limiting toxicities in everolimus therapy. Severe and painful oral mucositis results in a difficulty in taking food and drink and impairs patient's quality of life (QOL) (de Oliveira et al. 2011; Rugo et al. 2014), which may lead to the discontinuation of the therapy. Therefore, it is extremely important to provide comprehensive supportive care for prophylaxis or relief of AEs in patients receiving everolimus.

In our outpatient cancer chemotherapy clinic, oncology medical team consisting of physicians, nursing staff and pharmacists, including an oncology pharmacist, started to provide pharmaceutical care for prevention or cure of AEs associated with cancer chemotherapy. In the present study, we evaluated the effect of such pharmaceutical interventions on the incidence of AEs, patient's QOL and the duration of therapy in postmenopausal HR-positive advanced breast cancer patients receiving oral everolimus in combination with exemestane. Data were subsequently compared with those obtained before introduction of pharmaceutical intervention.

2. Investigations and results

2.1. Patients demographics

Characteristics of participants are shown in Table 1. No significant differences were observed between the intervention group and non-intervention group. In one patient in the intervention group who underwent hemodialysis, initial dose of everolimus was 5 mg.

2.2. Incidence of AEs associated with everolimus and exemestane

After pharmaceutical intervention, no reduction in the adherence was observed for everolimus and exemestane combination therapy. Incidence and grade of AEs are listed in Table 2. The incidence of grade ≥ 2 oral mucositis was significantly (p<0.001) lower in the intervention group (6/31, 19.4%) than in the non-intervention group (6/6, 100%). Discontinuation of treatment due to the incidence of severe oral mucositis was observed in 3 of 6 patients (50%) in the non-intervention group and one of 31 patients (3.2%) in the intervention group (Table 3).

Table 1: Characteristics of patients

	Before intervention group (n=6)	After intervention (n=31)	p value
Median age, years (range)	65.0 (55–72)	60.0 (39–78)	0.301[a)]
Performance status (ECOG; mean, range)	0.17 (0–1)	0.35 (0–2)	0.615[a)]
0/1/2/3	5/1/0/0	22/7/2/0	
Common sites of metastases, n			
Lung/Lymph nodes/liver/bone/brain	2/3/3/4/0	21/17/13/19/3	0.818[b)]
No. of metastatic sites, n			
1/2/≥3	1/2/3	3/7/21	0.506[a)]
No. of previous therapies , n			
1/2/≥3	0/0/6	1/5/25	0.500[b)]
Most recent previous treatment			
Letrozole or anastrozole used in combination with chemotherapy, n	6	28	0.579[c)]
Letrozole or anastrozole used alone, n	0	3	
Starting doses, n 10mg / 5 mg	6/0	30/1	1.000 [c)]

[a)] Mann-Whitney U-test, [b)]chi-square test, [c)]Fisher's exact probability test

Table 2: Incidence of major adverse events associated with everolimus plus exemestane before and after pharmaceutical intervention

	Before intervention group (n=6)			After intervention (n=31)			p value
	All grades	Grade 3-4 n	Grade ≥2 n	All grades n	Grade 3-4 n	Grade ≥2 n	
Non-hematological							
Oral mucositis	6	4	6	23	1	6	<0.001
Rash	3	1	2	19	0	5	0.316
Diarrhea	0	0	0	4	0	1	1.000
Fatigue	2	2	2	17	0	2	1.000
Dysgeusia	1	0	1	13	0	6	1.000
Interstitial pneumonia	1	0	1	10	0	4	1.000
Epistaxis	1	0	1	4	0	0	0.162
Hematological							
Platelet count decreased	1	0	1	6	0	2	0.422
Anemia	0	0	0	8	2	4	1.000

AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse events v4.0 (NCI/CTCAE v4.0).
Data were statistically compared by Fisher's exact probability test .

Table 3: Causes of discontinuation in patients receiving everolimus/exemestane therapy

Causes of therapy discontinuation	Before intervention (n=6)		After intervention (n=31)		p values
	n	%	n	%	
Progressive disease	2	33.3	11	35.5	1.000
Adverse events	4	66.7	6	19.4	0.0347
Oral mucositis (grade≥3)	3	50.0	1	3.2	0.00961
Interstitial pneumonitis (grade≥2)	1	16.7	4	12.9	1.000
Anemia by gastrointestinal bleeding (grade≥3)	0	0.0	1	3.2	1.000

Data were statistically compared by Fisher's exact probability test .

In the non-intervention group, supportive care was carried out in case severe oral mucositis occurred. Emergency admission due to the incidence of severe oral mucositis occurred in one patient in the non-intervention group but not observed in the intervention group.
On the other hand, the incidence rates of other AEs were not significantly different between the two groups. Grade > 2 interstitial pneumonia developed in 4 patients (12.9%) in the intervention group and one patient (16.7%) in the non-intervention group, regardless of careful diagnosis and management of the interstitial pneumonia.

2.3. Health-related QOL states in the pharmaceutical intervention group

Among 31 patients in the intervention group, QOL could be evaluated monthly for 6 months in 10 patients, however, the remaining 21 patients were unable to be assessed due to the lack of patient's consent, disease progression and so on. The mean EQ-5D-5L health states in the intervention group were not significantly changed during 6 months (p=0.359 by repeated measure one-way ANOVA), in which the values were 0.8644±0.0818 (mean±SD) in the first

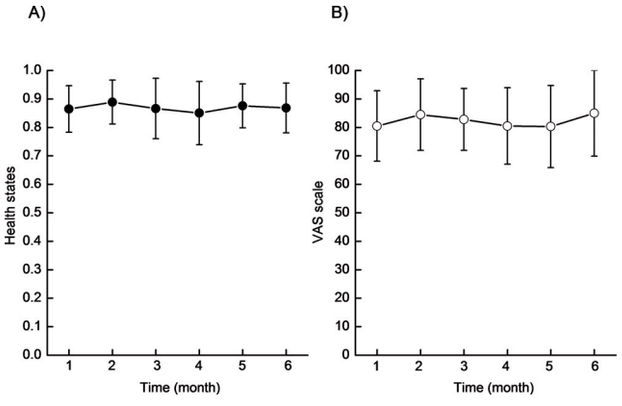

Fig. 1: Changes in the mean EQ-5D-5L health states (A) and VAS scores (B) during 6 months after treatment with everolimus in combination with exemestane for breast cancer. Each symbol represents the mean ± SD of 10 patients. Data were analyzed by repeated measure one-way ANOVA (Mauchly's sphericity test).

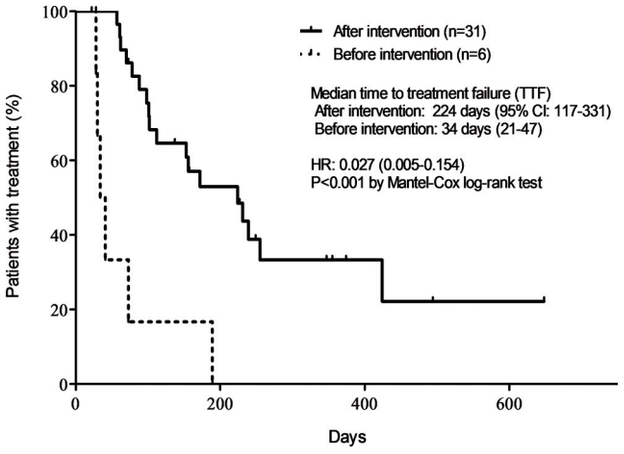

Fig. 2: Kaplan-Meier plots for comparison of time to treatment failure (TTF) between the pharmaceutical intervention group and non-intervention group. Median TTF was 224.0 days (95% confidence interval, CI: 117-331) for pharmaceutical intervention group, and 34.0 days (21-47) for non-intervention group (Hazard ratio: 0.027, 95% CI: 0.005-0.154, p<0.001 by Mantel-Cox log-rank test).

month, 0.8889±0.0774 in the second month, 0.8663±0.1064 in the third month, 0.8502±0.1111 in the fourth month, 0.8757±0.0774 in the fifth month, and 0.8682±0.0872 in the sixth month (Fig. 1A). In addition, no significant changes in the time course of the mean VAS scores were also observed (p=0.423 by repeated measure one-way ANOVA), where the scores were 80.5±12.3 in the first month, 84.5±12.6 in the second month, 82.8±10.9 in the third month, 80.5±13.4 in the fourth month, 80.3±14.4 in the fifth month, and 85.0±15.1 in the sixth month (Fig. 1B).

2.4. Time to treatment failure (TTF)

As shown in Table 3, all 6 patients discontinued the therapy in the non-intervention group due to disease progression (n=2), incidence of oral mucositis (n=3) and interstitial pneumonia (n=1), while 17 of 31 patients (54.8%) ceased the therapy due to disease progression (n=11), incidence of oral mucositis (n=1), interstitial pneumonia (n=4), and gastric bleeding (n=1). Therefore, the incidence of severe oral mucositis was the major cause of discontinuation of therapy in the non-intervention group (50%) but not in the intervention group (3.2%, p=0.00961). As shown in Fig. 2, median TTF was significantly longer in the intervention group (224.0 days, 95% confidence interval: 117 – 331 days) than in the non-intervention group (34.0 days, 21-47 days) [hazard ratio (HR): 0.027, 95% confidence interval: 0.005 – 0.154, p<0.001 by Mantel-Cox log-rank test].

3. Discussion

In the present study, patients receiving everolimus in combination with exemestane revealed a number of moderate to severe AEs, including oral mucositis, rash, fatigue, interstitial pneumonitis, dysgeusia and epistaxis, some of which may lead to the impairment of QOL and reduced adherence to drug therapy. Comprehensive pharmaceutical care for prevention of severe AEs was provided to patients receiving everolimus and exemestane. We found that such pharmaceutical intervention was effective in reducing the incidence of grade ≧2 AEs, particularly for oral mucositis. Before implementation of comprehensive pharmaceutical care, patients showing grades 1-2 oral mucositis were not treated with either saline gargle containing azulene sodium sulfate, topical steroid or oral care, thus grade 3-4 symptoms occurred in 4 of 6 patients (67%). However, prophylactic treatment with saline gargle containing azulene sodium sulfate in combination with oral care was carried out after pharmaceutical intervention. In addition, a topical steroid was prescribed when grade 1 symptoms appeared. As a consequence, the incidence of grade 3-4 oral mucositis was markedly reduced to 3.2% (1/31). Baselga et al. (2012) showed in breast cancer patients receiving everolimus and exemestane that the incidence of severe (grade 3-4) oral mucositis is 8%. Hatano et al. (2016) reported in Japanese patients receiving everolimus that 91% of patients revealed any grade of oral mucositis, in which grade 3-4 was observed in 2%. In addition, Peterson et al. (2016) showed that the incidence of oral mucositis after administration of everolimus is 44–78% for all grades and 4–9% for grade 3-4 symptoms. Our data on the incidence of grade 3-4 oral mucositis after implementation of preventive measures (1/31, 3.2%) was almost comparable to or rather somewhat lower than those reported earlier. On the other hand, one of 6 patients in the non-intervention group required an emergency hospitalization due to the incidence of grade 3 oral mucositis that restricted oral intake, whereas no emergency admission was observed in the intervention group. However, the incidence rates of other AEs were not significantly different between the intervention group and non-intervention group. The incidence of interstitial pneumonitis associated with mTOR inhibitors is reported to be 4-11% (Molas-Ferrer et al. 2013) or up to 25% (White et al. 2009), although there has been no effective treatment other than cessation of therapy followed by high-dose steroid treatment for prevention of severe interstitial pneumonitis. In the present study, the incidence rate of grade ≥ 2 interstitial pneumonitis was not significantly different between the non-intervention group and the intervention group (17%, one of 6 patients *versus* 13%, 4 of 31 patients, p=1.00).

The QOL health states as assessed by EQ-5D-5L questionnaire and VAS were moderate, in which the health state was 0.8644±0.0818 (mean±SD) and VAS score was 80.5±12.3 at the first month, and the values were almost constant during the 6 month treatment periods.

It has been demonstrated in patients with stage IV non-small cell lung cancer that improvement of QOL by the implementation of early palliative care is associated with prolongation of overall survival (Temel et al. 2010).

Moreover, the present pharmaceutical intervention seemed to be useful to maintain drug adherence, since no patient in the intervention group showed nonadherence to the everolimus therapy throughout the study period. It has been demonstrated that poor adherence to imatinib, an inhibitor of BCR/ABL kinase used for the therapy of chronic myeloid leukemia, results in worse treatment outcome (Ibrahim et al. 2011; Marin et al 2010). The importance of pharmaceutical monitoring for the maintenance of drug adherence in patients receiving oral anticancer drugs has also been shown by Ribed et al. (2016).

It was notable in the present study that the median TTF was much longer in the intervention group than in the non-intervention group (224 days *versus* 34 days, p<0.001). The major cause of therapy discontinuation was the incidence of severe oral mucositis in the non-intervention group, while only one of 31 patients (3.2%) stopped the therapy because of the incidence of severe oral mucositis. Therefore, prevention or amelioration of oral mucositis

may contribute at least in part to the prolongation of the treatment period. Moreover, it is suggested that the continuation of therapy by the pharmaceutical intervention may lead to an improvement of clinical outcomes in breast cancer patients receiving everolimus, although the overall survival was not significantly different between the two groups in the present study.

There are several limitations in the present study: first, this was a single-institutional non-randomized before and after study. Second, sample size was too small. Third, subjects were limited to breast cancer patients who received everolimus in combination with exemestane. Fourth, no QOL data existed before implementation of pharmaceutical care.

In conclusion, comprehensive pharmaceutical care was provided to breast cancer patients receiving everolimus and exemestane in our outpatient cancer chemotherapy clinic. Pharmacists consulted with patients before examination by physicians to provide comprehensive pharmaceutical care. The incidence of severe oral mucositis was significantly reduced after provision of pharmaceutical care. Patients' health states determined by EQ-5D-5L was almost constant during 6 months after intervention. Non-adherence was not observed after implementation of pharmaceutical care. As a consequence, median TTF was significantly longer in patients receiving pharmaceutical care than in those without it.

4. Experimental

4.1. Patients and treatments

Subjects were 6 and 31 outpatients with advanced or recurrent breast cancer receiving oral everolimus in combination with exemestane before (during a period between April 2014 and June 2014) and after (during June 2014 and January 2016) pharmaceutical intervention, respectively. Everolimus (10 mg) and exemestane (25 mg) were administered orally once daily. Dose or administration of everolimus was modified according to the manufacturer's guide for appropriate use of the drug, if moderate to severe AEs appeared. The therapy was continued until disease progression or the occurrence of intolerable AEs.

4.2. Statement of ethics

All clinical investigations were approved by the Clinical Ethics Committee at the International Medical Center, Saitama Medical University (approved no. 14-134), and informed consent for participation was obtained from each patient (in the intervention group).

To protect the privacy of patients, personal information was anonymized in a linkable fashion for the data analysis. Patients' personal information could not be identified, and there was no disadvantage to patients participating in this study.

Conflicts of Interest: All authors have declared no conflicts of interest.

4.3. Measurement of health-related quality-of-life (QOL)

The health-related QOL of patients was investigated by using self-reported five-level version of EuroQol five-dimensional questionnaire (EQ-5D-5L) data based on the discrete choice experiment (DCE) and composite time trade-off (cTTO) data collected by computer-based survey reported by Shiroiwa et al. (2016), in which the value sets of EQ-5D-5L data, including motility, self-care, usual activities, pain/discomfort, and anxiety/depression, were converted to the QOL scale from 0 (death) to 1 (full health) by using the coefficients reported by the mixed model based on the cTTO and DCE data. A vertical 0-100-point visual analogue scale (VAS) was also used for rating the overall health status. The QOL assessment was carried out every month. To minimize the influence of bias, questionnaires and VAS were collected by a designated box at another location, and an investigator other than the medical staff who provided the explanation was responsible for the data analysis.

4.4. Pharmaceutical interventions

Pharmacists, including an oncology pharmacist, carried out interviews with a patient in a separate room during the time until examination by the physician after blood collection. All data obtained by the pharmacist on the symptoms, adherence to drugs, and presence or absence of AEs were entered in the electronic medical record to share information among different healthcare professions. Pharmacist offered a proposal on the prescription to the physician, if patients complained moderate to severe AEs, particularly oral mucositis, diarrhea, and interstitial pneumonia. For prevention of oral mucositis, the status of oral care, including the frequency and the method of brushing of teeth, was checked. If necessary, the need for the dental examination was immediately reported to the attending physician. At the start of everolimus and exemestane administration, preventive measures against oral mucositis, including regular gargling with saline containing azulene sodium sulfonate, were suggested to the attending doctor (Arakawa-Todo et al. 2013; Shida et al. 2014). When some signs of oral mucositis progressed to grade >1, topical steroid ointment was recommended to use. If the symptom shows no improvement, the pharmacist suggested to the physician prescribing the gargle containing *hangeshashinto* (Kono et al. 2014; Matsuda et al. 2015), a kampo herbal medicine, or polaprezinc, an anti-ulcer drug showing mucoprotective action (Hayashi et al. 2014). For prevention of interstitial pneumonia, the absence of a history of lung disease was checked before the start of chemo-hormone therapy. Patients were instructed by the pharmacist to pay attention to the early signs of interstitial pneumonia such as cough, shortness of breath, and fever. Patients who had any of such symptoms were requested to measure the body temperature and oxygen saturation at home daily to record the data on the patient's daybook and to make a telephone call to the hospital. Chest X-rays and CT scans were necessary before and after the chemo-hormone therapy. KL-6, C-reactive protein (CRP) and other blood test were examined if required. For prevention of diarrhea, patients were instructed to take a lactobacillus preparation (Bowen et al. 2007) regularly from the start of chemo-hormone therapy for prevention of diarrhea. Loperamide (Benson et al. 2004) was also prescribed for use when required. The appropriate use of such drugs was explained by the pharmacist. The status of bowel movements was checked during chemo-hormone therapy. If continuous diarrhea or loose stools occurred, the pharmacist made a proposal on the use of *hangeshashinto* (Yamaguchi et al. 2015) to the physician.

When a new drug was prescribed, the pharmacist provided an instruction on the use of the drug to the patient. The above-mentioned pharmaceutical care was offered to ensure that patients are free of AEs and take a proactive stance to the therapy.

4.5. Evaluation of drug adherence

Adherence regarding everolimus, exemestane, and other drugs was evaluated from the patient's daybook on every patient visits. The daybook, which was provided by the manufacturer for breast cancer patients receiving everolimus to record drugs taken and AE symptoms on a daily basis, was provided by the pharmacist on the first visit. The pharmacist continuously provided supportive care and drug administration guidance to patients and confirmed patient awareness and knowledge regarding AEs, symptom management, and drug adherence.

4.6. Grading of AEs

AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

4.7. Statistical analyses

Data were analyzed by using the Statistics Program for Social Science for Windows (SPSS-II version 11; SPSS, Chicago, IL, USA) and statistically compared before and after implementation of pharmaceutical care. Data were compared by parametric analysis (*t*-test) or non-parametric analysis, Mann-Whitney U-test or Fisher's exact probability test. Multiple parameters were compared between two groups by chi-square test. Time to treatment failure (TTF) was calculated by the Kaplan-Meier method (Kaplan and Meier 1958) and compared between the intervention and non-intervention groups by the log-rank test. A repeated-measures one-way analysis of variance (ANOVA) was carried out to compare time course changes in the EQ-5D-5L health states and VAS scores (Mauchly's sphericity test). A p value of less than 0.05 was regarded as statistically significant.

Conflicts of interest: None declared.

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