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Cost utility analysis of pharmacist counseling care for breast cancer chemotherapy outpatients

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Chemotherapy for cancer is increasingly implemented in the outpatient setting. Pharmacists contribute to cancer treatment by conducting counseling during outpatient chemotherapy visits. They provide guidance on drug treatment, side effects, and side effect countermeasures on every visit. However, there have been few economic evaluations of pharmacist involvement in outpatient chemotherapy. Therefore, we performed a cost utility analysis. We assigned usual care (control) and pharmacist counseling to two groups of 19 patients receiving outpatient chemotherapy for breast cancer at Gifu Municipal hospital. Quality of life was measured at three timepoints before and during chemotherapy treatment using the EuroQol 5 dimension instrument (EQ-5D). EQ-5D values across the timepoints were 0.831, 0.757, and 0.791 for the control group, and 0.882, 0.883, and 0.921 for the pharmacist counseling group. The additional cost in the pharmacist counseling group was 2,227 yen per counseling session. The change in quality-adjusted life years (QALY) was a maximum of -0.021±0.186 in the control group and 0.007±0.199 in the pharmacist counseling group. The maximum cost for one QALY was 1,360,558 yen (≈12,460 US dollars). Pharmacists' counseling in outpatient cancer chemotherapy for breast cancer patients had an acceptable incremental cost-effect ratio, contributing to improved patient quality of life without significant additional expenditure to healthcare.

1. Introduction

Chemotherapy for breast cancer treatment requires dose optimization because a higher than required dose often results in unpleasant and debilitating side effects. However, there are reports that the serious adverse effects associated with chemotherapy of women with breast cancer are more frequent than those reported in large scale clinical trials, resulting in more patient burden than previously estimated (Hassett et al. 2006). Patients are faced with the task of understanding complicated chemotherapy regimens, their potential side effects, and how to cope with these side effects.

Breast cancer chemotherapy is generally performed at outpatient clinics (Kitada et al. 2006). Outpatient chemotherapy has the advantage that treatment causes less disruption to patients' work and lifestyle, but unlike treatment with hospitalization, patients will not meet medical staff except on days of chemotherapy treatment, so it is difficult for them to consult medical staff easily. Therefore, patients need to deal with side effects and use supportive medications themselves.

Acceptance of treatment is largely based on the reality of breast cancer being a terminal condition without chemotherapy. Patient understanding of how chemotherapy can be made less debilitating with support medication is fundamental in building a concordant relationship. For this reason, it is important for medical staff to give explanations to patients before starting chemotherapy, and to accurately provide guidance by examining the patient's condition after starting chemotherapy (Dodd 1988).

Pharmacists have become involved in outpatient cancer chemotherapy in recent years, and support the medical treatment by explaining and monitoring the side effects of chemotherapeutic drugs, devising and suggesting side-effect treatment medicines, and providing guidance on how to use coping medicines.

Many benefits of pharmacist engagement in outpatient cancer chemotherapy have been reported. Several reports have found increased treatment effect and reduced side effects as a result of pharmacists teaching patients in the outpatient setting. There are several clinical outcomes reported for pharmacist involvement in outpatient chemotherapy (Shah et al. 2006; Randolph et al. 2015), but we could not find reports evaluating patient benefits of pharmacist involvement from an economic perspective.

Traditionally, the Japanese hospital pharmacist was responsible for dispensing medicine from the pharmacy department. However, in recent years pharmacists have taken on additional roles required from the clinical side. Pharmacists now support patients with medicines, and doctors and nursing staff through pharmaceutical care in wards and outpatient departments. This new work for pharmacists is caused by the social needs and desires of medical facilities, but cost effectiveness has not been adequately considered (Fujii et al. 2006). In some countries including England, whether or not new therapeutic drugs or technologies have benefits worth their additional costs is assessed by various evaluation facilities, and only cost-effective products and services are introduced to the clinic.

As pharmacists participate in outpatient cancer chemotherapy, additional costs including personnel expenses will be incurred, but cost-effectiveness analyses are required to clarify whether these additional costs are commensurate with the positive effects. Therefore, we performed a medical economic evaluation of pharmacists providing counseling to patients undergoing outpatient chemotherapy for breast cancer.

2. Investigations and results

All results are expressed in the following format: usual care (control) group value, pharmacist counseling group value.

2.1. Patient attributes

Participants with breast cancer were assigned to treatment groups according to when their first outpatient chemotherapy course was

initiated, 19 patients were assigned to the control group and 19 patients were assigned to the pharmacist counseling group. All patients were women (mean ages 53.37 years and 56.74 years). In the pharmacist counselling group, pharmacists counselled patients before chemotherapy administration on the first day of patients' first three chemotherapy courses. All patients had a performance status (PS) of 0 and most patients in the two groups had stage 2 cancer: 42.1 % and 57.9 %. Human epidermal growth factor receptor type 2 (HER2) expression was positive for 26.3 %, 25.0 %; estrogen receptor (ER) was positive for 78.9 %, 75.0 %; and progesterone receptor (PgR) was positive for 52.6 %, 55.0 % of the patients. Most patients (57.9 % and 68.4 %) were administered a regimen of epirubicin plus cyclophosphamide. There were no significant differences between the control group and the pharmacist counseling group for any patient attribute ($P > 0.05$). Patient attributes are shown in Table 1.

Table 1: Patient attributes

Item		UC	PC	*P*
Age (year)				
Mean ± Standard deviation		53.4±11.1	56.7±9.0	0.313
Gender				
	Female / Male	19 / 0	19 / 0	1.000
PS	0 / 1 / 2	19 / 0 / 0	19 / 0 / 0	1.000
Stage	I / II / III / IV	3 / 8 / 5 / 3	6 / 11 / 2 / 0	0.124
HER2	0 / +1 / +2 / +3	1 / 9 / 6 / 3	1 / 11 / 2 / 5	0.269
ER	+ / ± / -	15 / 2 / 2	14 / 4 / 1	0.596
PgR	+ / ± / -	10 / 4 / 5	10 / 5 / 4	0.774
Regimen				
Anthracyclines (EC / FEC)		11 (11 / 0)	13 (11 / 2)	0.196
Taxanes (TC / nabPTX / PTX+B)		5 (3 / 1 / 1)	6 (6 / 0 / 0)	
Others (CMF)		3 (3)	0 (0)	

Fisher's exact test, PS: performance status, HER2: human epidermal growth factor receptor type 2, ER: estrogen receptor, PgR: progesterone receptor, EC: epirubicin/cyclophosphamide, FEC: fluorouracil/epirubicin/cyclophosphamide, TC: docetaxel/cyclophosphamide, nab-PTX: nanoparticle albumin-bound paclitaxel, PTX: paclitaxel, BV: Bevacizumab CMF: cyclophosphamide/methotrexate/fluorouracil

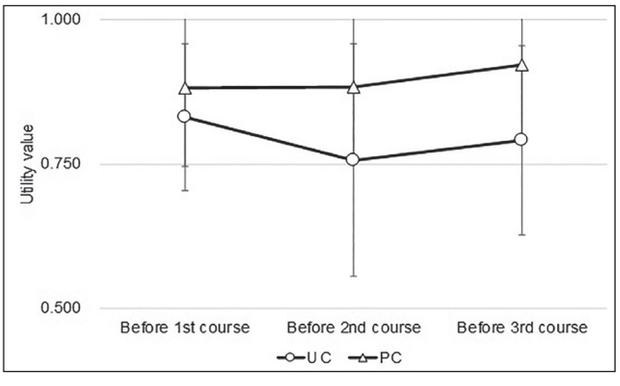

Fig. 1: Change of utility value in both groups.

2.2. Utility value

The EuroQol 5 Dimension (EQ-5D) instrument was used to measure quality of life (QOL) and this was taken as the utility value. EQ-5D assessment was performed before chemotherapy administration on the first day of patients' first three chemotherapy courses. Utility values were as follows: before first chemotherapy course 0.831±0.127, 0.882±0.136; before second course 0.757±0.201, 0.883±0.128; and before third course 0.791±0.164, 0.921±0.122 (Fig. 1). There was no significant difference in utility value before the first chemotherapy course between treatment groups, but the counseling group had significantly higher utility value before the second and third courses (Table 2).

Table 2: Utility value of both groups

		Before 1st course		Before 2nd course		Before 3rd course	
Group	N		*P*		*P*		*P*
UC	19	0.831±0.127	0.237	0.757±0.201	0.027*	0.791±0.164	0.009*
PC	19	0.882±0.136		0.883±0.128		0.921±0.122	

unpaired t-test, *$P < 0.05$, mean±standard deviation

2.3. Change in quality of life

Over six months, the gradient for change in QOL calculated from the onset of treatment to: before the second chemotherapy course was 0.300±0.183, 0.394±0.148; before the third course was 0.353±0.114, 0.445±0.089; the mean value before the second and third courses was 0.315±0.146, 0.419±0.108. Over one year, the gradient for change in QOL calculated from the onset of treatment to: before the second course was 0.538±0.423, 0.745±0.372; before the third course was 0.604±0.328, 0.853±0.272; the mean value before the second and third courses was 0.540±0.357, 0.788±0.316.

2.4. Difference in quality-adjusted life years

Over six months, the change in quality-adjusted life years (QALY) calculated from the onset of treatment to: before the second chemotherapy course was -0.028±0.097, -0.007±0.099; before the third course was -0.060±0.109, 0.004±0.107; the mean value of before the second and third courses was -0.047±0.099, -0.012±0.119. Over one year, the change in QALY calculated from the onset of treatment to: before the second course was -0.021±0.186, 0.007±0.199; before the third course was -0.100±0.193, 0.022±0.207; the mean value of before the second and third courses was -0.090±0.233, 0.005±0.219.

2.5. Additional cost

Drug expenses and treatment fees required for cancer chemotherapy did not differ between patient backgrounds and chemotherapy regimens, so we assumed that these costs were equal in both groups. The hourly wage of the pharmacist was 2,227 yen according to the basic statistical survey on wage composition by the Ministry of Health, Labor and Welfare. In this study, as most regimens were administered every three weeks, pharmacists also counseled every three weeks, prior to each intravenous chemotherapy treatment. Assuming that pharmacists continued to counsel at this frequency, we estimated that a pharmacist would counsel eight times in six months and seventeen times in one year for each patient. Therefore, pharmacist involvement in cancer chemotherapy increases costs by 17,816 yen over 6 months for one patient, and by 37,859 yen over one year for one patient.

2.6. Incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio (ICER) produced by dividing the increased cost by the QOL area difference between the control group and the pharmacist counseling group over six months using the values from: before the second chemotherapy course was 860,711 yen per QALY, before the third course was 279,351 yen per QALY, and the mean of before the second and third courses was 511,141 yen per QALY. Over one year, ICER calculated using the values from: before the second course was 1,360,558 yen per QALY, before the third course was 312,728 yen per QALY, and the mean of before the second and third courses was 401,400 yen per QALY (Table 3).

Table 3: QALY gain of each model

Model Utility value gradient	Period	Group	N	QALY change average±SD	Increase cost (yen)	ICER (yen/QALY)
1st course	6 month	UC	19	-0.028±0.097	0	860,711
		PC	19	-0.007±0.099	17,816	
2nd course	6 month	UC	19	-0.060±0.109	0	279,351
		PC	19	0.004±0.107	17,816	
Middle of 1st and 2nd course	6 month	UC	19	-0.047±0.099	0	511,141
		PC	19	-0.012±0.119	17,816	
1st course	1 year	UC	19	-0.021±0.186	0	1.360,558
		PC	19	0.007±0.199	37,859	
2nd course	1 year	UC	19	-0.100±0.193	0	312,728
		PC	19	0.022±0.207	37,859	
Middle of 1st and 2nd course	1 year	UC	19	-0.090±0.233	0	401,400
		PC	19	0.005±0.219	37,859	

3. Discussion

In this study, we investigated the cost-effectiveness of pharmacist counseling for patients who undergo outpatient chemotherapy for breast cancer using EQ-5D as the utility value.

For the three models over both six months and one year, the ICER was lowest when estimated with QOL measured after the second chemotherapy course, and highest when estimated with QOL after the first course. In the case of breast cancer chemotherapy, side effects from the first chemotherapy treatment often cause a large decrease in QOL (Tanaka et al. 2018). However, the second chemotherapy course improves QOL through dosage reduction and side effect countermeasures depending on the severity of side effects for the patient. Therefore, the ICER derived using QOL measured after the first chemotherapy course (which causes a large decrease in QOL) was largest, and the ICER obtained using QOL measured after the second course (when QOL improved due to countermeasures) was the smallest. The ICER estimated using the mean QOL measured after the first and second courses was intermediate for both the six month and one-year periods.

Evaluation of the economic cost and cost-effectiveness of health care interventions is important to justify implementing new interventions, especially in countries where economic resources for public health care services are limited. We used cost utility analysis as it is the most reliable method to evaluate the effect of an intervention on cost-effectiveness. Measuring the utility value using the patients' reported outcomes allows more accurate analysis.

For the pharmacist counseling group there was no decrease in QOL after the initiation of cancer chemotherapy, and chemotherapy was performed with higher QOL than in the control group. The results of the present study indicate that pharmacist counseling did not increase economic expenditure significantly and had an acceptable ICER of at most 1,300,000 yen per QALY. The results suggest that even in a country with limited economic resources, introducing pharmacist counseling for outpatient cancer chemotherapy is economically viable because it did not add significant costs over usual care yet it improved QOL significantly.

To the best of our knowledge, a cost utility analysis comparing pharmacist interventions with usual care has not been published for cancer chemotherapy. However, for other diseases such as chronic obstructive pulmonary disease (COPD) and depression, there are reports comparing pharmacist intervention with usual care using cost utility analysis.

In a report on COPD by Khdour et al. (2011) the average EQ-5D utility value was high in the baseline control group, but higher in the pharmacist counselling group after both six months and one year. Khdour et al. (2011) reported that the educational program for COPD patients had an ICER of 3,278 pounds (≈4,212 US dollars) per QALY. The pharmacist counselling group appeared to be at an advantage, but no statistically significant difference was observed (Khdour et al. 2011). Pharmacist involvement resulted in reduced disease progression during treatment, thus increasing utility value, which is consistent with our results. The average utility value of patients with COPD, as reported by Gore et al. (2000), is lower than that of our patients with cancer. We consider these to be disease-specific differences as patients with COPD do not access the special care system available to patients with cancer (Gore et al. 2000). Rubio-Valera et al. (2013) reported on pharmacist intervention for patients with depression; pharmacists instructed outpatients to improve their knowledge of side effects and the importance of compliance, and the ICER for pharmacist intervention compared with usual care was 9,872 euros (≈11,322 US dollars) per QALY.

For interventions involving pharmacists with other diseases, as in our study, there are many reports that costs are less than five million yen per QALY. Thus, pharmacist intervention has low cost and improves utility. If pharmacist counseling results in drug prescriptions to cope with the side effects of patients, drug costs will increase, but many drugs are used for short periods until side effects disappear. Depending on the adverse reactions, there are side effects which can be dealt with ingenuously in daily life, in which case only guidance by a pharmacist is required, with no additional drug costs incurred. Furthermore, as pharmacists are involved, drugs owned by patients are noted, prescription of overlapping drugs may be prevented, and drug cost may be reduced. Based on these facts, while pharmacist counseling always requires personnel expenses for the pharmacist, there are few other costs.

This study highlights that one effective method of maintaining QOL at low cost for chemotherapy outpatients is to provide pharmacist counseling so that patients have sufficient knowledge and ability to manage their own side effects. Hospital pharmacists can potentially play an important role in the delivery of such guidance as they are in a primary position to teach the skills needed to carry out chemotherapy and side effect treatment, and indeed treatments for other diseases.

Economic evaluations are highly affected by sample variability. This study was conducted in a single facility, and the number of samples was small. Novel chemotherapy treatments are developed annually; therefore, there is a possibility that the standard therapy in a clinic may be replaced, so the research period cannot be long enough to obtain comparable samples. However, there was no difference in attributes between the two patient groups, and the patient statistics of the Japan Breast Cancer Society and the sample composition of this study were equivalent.

This study measured QOL early in cancer chemotherapy, but treatment with cancer chemotherapy continues for six months or longer in many cases. The accurate QALY can be measured by actually conducting a QOL survey at the completion of cancer chemotherapy, but it is very difficult to follow patients to completion due to variation in cancer progression and patient condition.

Careful discussion is required as to whether a QOL survey conducted early in chemotherapy is optimal, but this research is extremely beneficial in that the economic utility of pharmacist counseling was confirmed in all our models.

4. Experimental

4.1. Patients and treatment period

The participants were 38 patients with breast cancer who received their first course of intravenous outpatient chemotherapy at Gifu Municipal Hospital between December 2013 and November 2015. None of the patients received hormone monotherapy or radiation therapy. All patients received appropriate chemotherapy according to the clinical practice guidelines for breast cancer and appropriate supportive therapy according to the guidelines for antiemesis.

4.2. Assignment

Patients beginning treatment in the first half of the research period were assigned to the usual care group without pharmacist involvement (control), and patients beginning treatment in the second half were assigned to the pharmacist-counselled group (Fig. 2).

4.3. Pharmacist involvement

The pharmacist provided personal counseling before chemotherapy was performed on the first three days of intravenous chemotherapy administration. In pharmacist counseling before the first chemotherapy course, the pharmacist explained the side effects of chemotherapeutic agents, how to deal with the side effects, and how to use supportive medicines. The pharmacist conducted personal counseling in accordance with patients' conditions and their degree of understanding. In pharmacist counseling after the first chemotherapy treatment, the pharmacist listened to the patient's experience of side effects and decided on medication according to these side effects and proposed appropriate prescriptions to the doctor. Counseling was conducted by a pharmacist who had over five years' experience of cancer chemotherapy and had completed training in oncology.

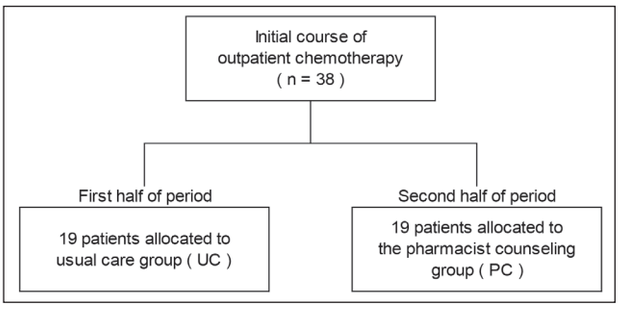

Fig. 2: Flowchart of the study population.

4.4. Survey items

Survey items were patient attributes, treatment regimen, and QOL. Patient attributes and treatment regimens were obtained from patients' electronic medical records including age; Stage; PS; HER2, ER, and PgR expression status. QOL was measured using a self-completed questionnaire before the first, second, and third courses of outpatient chemotherapy (day one of each course immediately before chemotherapy administration). QOL was assessed using the EQ-5D instrument (EuroQol, 1990). EQ-5D is a standardized instrument for measuring health status, and its reliability and validity have been confirmed for Japanese people (Okamoto et al. 2004). Health status measured with EQ-5D was taken as the utility value, then by combining utility value with time, we calculated QALY.

4.5. Sensitivity analysis

In clinical practice, breast cancer chemotherapy often continues for a period of six months or more. However in this study, since we surveyed up to the third course of cancer chemotherapy, we only investigated the influence of pharmacist counseling in early treatment stages. Using our QOL data, covering up to just before the third course, we calculated the area under the straight line assuming that the trends in QOL values continue for either six months or one year after the third course.

Although the area under this straight line can generally be taken as QALY, each QOL value measured at an early stage of cancer chemotherapy had a large influence on the area under the straight line, due to the small number of measurements. Therefore, in order to evaluate the influence of fluctuations in QOL measurements on QALY, the straight line (and area under it) was calculated using three different endpoints: we draw three lines with inclination of AB, AC, and AD, starting from A, with A = before the first course, to B = before the second course, C = before the third course, and D = the mean of before the second and third courses (Fig. 3).

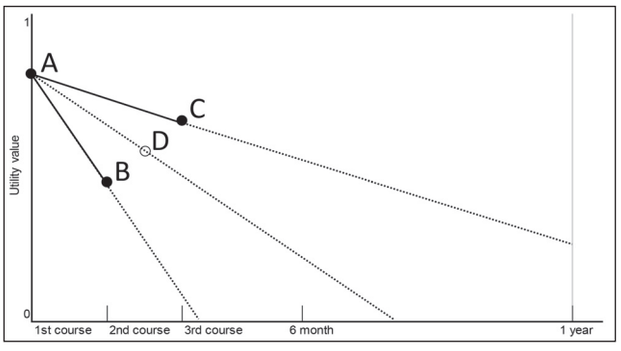

Fig. 3: Actual measurement utility value and estimated QALY area. A, B and C are measured utility values of EQ-5D. D is an intermediate utility value between the actually measured values B, C.

4.6. Analysis and statistical processing

Analysis was performed on the assumption that the gradients of the straight lines connecting QOL values described above continued for six months or one year. If the QOL trend line reached zero before six months or one year had elapsed, we took the area under the straight line up to that point. Similarly, if the QOL trend line reached one, the area under the straight line was calculated assuming that QOL remained as one until six months or one year after that point. Differences between treatment groups were analyzed using t-test, and p values below 0.05 were considered statistically significant.

4.7. Cost calculation

In the group counselled by the pharmacist, the time spent counseling by the pharmacist was calculated as an additional cost based on hourly wage. The hourly wage was estimated using the basic statistical survey on wage structure by the Ministry of Health, Labor and Welfare. Cost was calculated for one pharmacist counseling session per chemotherapy course. Counseling time was calculated assuming that it takes one hour in total including preparation, patient counseling, discussion with the attending physician, and record creation.

4.8. Incremental cost-effectiveness ratio

To evaluate the medical practice of pharmacist counseling, we compared the additional cost and additional QALY obtained with counseling. From the obtained values, based on the ICER method, we calculated the cost required to extend life by one QALY by dividing the additional cost by the change in QALY.

4.9. Ethics statement

This study was approved by the Ethical Review Board of Gifu Municipal Hospital (approval no. 186). Participants were given sufficient explanation of the study in writing including the following contents: purpose of the study, research method, subject of study, cost, ethical consideration, and management of personal information. After the explanation participants provided written informed consent.

Conflict of interests: The authors declare no conflict of interest.

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