anxiety score was 41.6. Kindler *et al.*[19] examined 734 patients one day before surgery, and their mean score was 39.0. Iwata *et al.*[20] examined 51 women just before surgery for varicose veins with local anesthesia, and their mean score was 45.6. In the present study, many participants (21/27 cases) reported that one of the causes of pre-surgical anxiety was the possibility of cancer. The STAI state anxiety score in this study was higher than in previous reports, indicating that fear of the possibility of ovarian cancer worsens pre-surgical anxiety.

The following specific risk factors related to psychological distress in ovarian cancer patients have been reported: young age,[8,9] progression of carcinoma, recurrence of tumor, short time from cancer diagnosis,[8] poor social support, history of physical disease and psychiatric disorders.[9] We assessed predictive factors, such as demographic data and the patients' character, but these did not predict adjustment disorder. The STAI trait anxiety score and MPI-N scale tended to be higher in the adjustment disorder group than the non-adjustment disorder group; however, these differences were not statistically significant. Although these results were in part due to the sample size, adjustment disorder might be difficult to predict by demographic factors or the participants' character, as has been previously reported. Further research is needed to elucidate the predictive factors for adjustment disorder. The probability of cancer mentioned in the pre-surgical explanation did not impact on the prevalence of adjustment disorder. Donovan *et al.*[21] reported that patient-provider communication affected symptom control in ovarian cancer patients. Although it cannot be denied that each patient–gynecologist relationship affects the patients' anxiety, the patient–gynecologist relationship in the current study was not evaluated by quantitative analysis. However, the attending physicians carefully explained to the participants based on the protocol before surgery, and most participants commented in the interviews on the kindness of their attending physicians. Both specific information about their disease and emotional support were reported to be necessary to reduce patients' psychological distress for cancer patients,[22,23] including ovarian[24,25] and cervical[26–28] cancer patients. Mishel[29] reported that uncertainty about their condition affects the patients' anxiety. In pre-surgical counseling of ovarian tumor patients, the explanation included uncertainty and vagueness about the cancer, because it is not possible to clearly determine whether or not the tumor is malignant. Patients' anxiety may be amplified more by this uncertainty than by the level of severity mentioned in the explanation of the probability of cancer before surgery for ovarian tumors. In the current study, it is notable that two-thirds of the participants recovered from adjustment disorder when they received their cancer diagnosis after surgery.

In the present study, the prevalence of adjustment disorder prior to the surgery among the patients who were finally diagnosed as having a benign tumor was similar to that among the malignant group. The participants reported that the possibility of cancer made them anxious; therefore, the adjustment disorder developed due to anxiety or fear of the possibility of cancer. McGovern *et al.*[30] described that patients who received false-positive results on the cancer screening test had emotional and health distress and felt a lower quality of life. In addition, many participants reported that they were shocked when they first heard that they had an ovarian tumor in the outpatient clinic. Patients who are found to have an ovarian tumor might have a high level of anxiety more than one day before the surgery. We must attend to the psychological distress of patients from the time of detection of ovarian tumors.

The mean STAI state anxiety score after surgery in the malignant group was higher than that in the benign group. In the benign group, the mean STAI state anxiety score decreased immediately after the patients learned that their tumor was benign. The majority of patients who were finally found to have ovarian cancer were diagnosed as having adjustment disorder (9/12 cases). The period of this study extended from shortly before surgery to just after surgery and before adjuvant chemotherapy was started. However, cancer patients were reported to be at risk for developing severe psychiatric disorders, such as depression[1,10] or PTSD[31] during or after their treatment. In the present study, patients who were diagnosed with ovarian cancer received an explanation about their cancer diagnosis, the necessity of chemotherapy and the risk of recurrence. Therefore, the object of their anxiety changed with the progression of the cancer. The ovarian cancer patients continued to feel anxiety throughout their lives, especially those patients who received adjuvant chemotherapy. We previously reported two ovarian cancer patients who developed PTSD after being diagnosed with ovarian cancer.[32] It may seem that this adjustment disorder is not as severe as other psychiatric disorders, such as depression and PTSD, but Cuijpers and Smit[33] reported that sub-threshold depression (patients with clinically relevant depressive symptoms, without meeting the criteria for a full-

blown major depressive disorder) is a risk factor for major depressive disorders. Therefore, patients who are diagnosed with adjustment disorder, especially those who are confirmed to have ovarian cancer, must be followed up intensively with regard to the progression of their psychological distress or psychiatric symptoms.

In this study, we showed that ovarian tumor patients awaiting surgery have a high level of anxiety. It is important to provide patients with pre-surgical information about their ovarian tumor, but we must deliberate on how to inform patients of the probability of ovarian cancer. However, in the present study, measurement of the severity of pre-surgical explanation was based on the attending physicians' report, and the quality or quantity of explanation may have been different for each physician; therefore, additional research is required to replicate this effort with objective measurement of the physicians' explanation.

In conclusion, we should consider and carefully monitor the psychiatric condition of patients during treatment of ovarian tumors, even in patients with benign disease. In ovarian cancer patients, especially those with adjustment disorder, long-term psychological follow-up is crucial.

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EPIDEMIOLOGY

The model-based cost-effectiveness analysis of 1-year adjuvant trastuzumab treatment: based on 2-year follow-up HERA trial data

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Abstract *Background* Several randomized controlled trials have confirmed the usefulness of trastuzumab as an adjuvant therapy for HER2-overexpressed breast cancer patients; however, the costs for 1-year treatment are high. Therefore, we performed an economic analysis regarding the efficient distribution of medical resources. *Methods* To analyze the cost-effectiveness for a 1-year adjuvant trastuzumab treatment group compared with the observation group, we constructed a Markov model adopting a 3% per year discount rate for costs and outcomes. The time horizon was 50 years. The perspective was that of health-care payers, as only direct medical costs were calculated. The outcome was measured as life-year gained (LYG) from 2-year follow-up HERA trial data. *Results* The ICER of the standard setting (5 years efficacy and 50–60 kg patient weight) was JPY 2,600,000 (€17,000) per LYG. The calculation results of other weight class ICER were JPY 2,200,000 (€15,000) and JPY 3,300,000 (€22,000) per LYG for the patients, respectively, who weighed less than 50 kg, and 60–75 kg. In the sensitivity analysis, the period of trastuzumab efficacy was the most influential parameter for the result of cost-effectiveness. However, even if the trastuzumab efficacy were to continue for only 2 years, at least, which is a conservative setting judging from the joint analysis (NSABP B-31 and NCCTG N9831 trials), the ICER remains acceptable for any weight class. *Conclusion* These results suggest that the 1-year adjuvant trastuzumab treatment is cost-effective. Both clinical and economic benefits were superior for the 1-year adjuvant trastuzumab treatment group compared with the observation group.

Keywords Adjuvant treatment · Breast cancer · Cost-effectiveness · HERA trial · Trastuzumab

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Introduction

In Japan, the number of patient deaths due to breast cancer is increasing, while breast cancer mortality in Europe and the USA has generally improved since the 1990s [1]. The death toll from breast cancer is estimated as 10,000 persons per year, and reducing deaths due to breast cancer is one of the most important issues for women's public health.

Trastuzumab (Herceptin®) is a humanized monoclonal antibody that selectively targets the human epidermal growth factor type-2 (HER2) receptor. Amplification of the HER2 gene and overexpression of the HER2 protein, considered to be poor-prognosis factors, are observed among 20–30% of breast cancer patients [2]. Trastuzumab administered as combination therapy with chemotherapy has been proved to significantly improve disease-free survival, overall survival, and health-related quality of life (QoL) for metastatic breast cancer patients [3–5]. After 2005, several randomized control trials (RCTs) have confirmed the usefulness of trastuzumab as adjuvant therapy for HER2-positive patients, not only as metastatic therapy.

Ongoing large multicenter adjuvant trastuzumab RCTs: 1) the Herceptin Adjuvant (HERA) trial [6, 7], 2) the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial [8], 3) the North Central Center Treatment Group (NCCTG) N9831 trial [8], and 4) the Breast Cancer International Research Group (BCIRG) 006 trial [9], have shown good results, whereby the hazard ratio of the recurrence rate was about 0.5 even for HER2-positive patients who had a poor prognosis.

Though the cost of adjuvant trastuzumab treatment is high, the National Institute for Health and Clinical Excellence (NICE) in the UK has recommended adjuvant trastuzumab treatment for HER2-positive breast cancer patients based on the 1-year follow-up data of HERA trial [6, 10]; however, no such recommendation exists in Japan, and there have been no results of cost-effectiveness analysis based on the 2-year follow-up data of the HERA trial [7].

Therefore, this cost-effectiveness analysis (CEA) is designed to examine the economic efficiency of adjuvant trastuzumab treatment based on the 2-year follow-up data of HERA trial to support societal decision-making.

Patients and methods

Economic analysis

To analyze the cost-effectiveness of adjuvant trastuzumab treatment compared with observation alone, we used the Markov model by which the most common clinical transitions and health state transitions were simulated from multiple data sources. The model was build by TreeAge Pro 2006 (TreeAge Software, Inc, Williamstown, MA). One Markov cycle length corresponded to 1 month.

We adopted a 3% discount rate per year for costs and outcomes [11]. The discount-rate range for sensitivity analysis was 0–6%. The time horizon was 50 years (i.e., 600 Markov cycles), meaning that essentially all patients are considered as being dead.

The analysis perspective was that of health-care payers, and we calculated only the direct medical costs by the piece, because we were interested in the impact on the medical costs of adjuvant trastuzumab therapy. Neither indirect costs (work loss, etc.) nor direct non-medical costs (transportation cost, etc.) were considered. The primary result is indicated as the incremental cost per incremental life-year-gained (LYG). We used the exchange rate of €1 = JPY 150.

Hypothetic patients

Patients eligible for the HERA trial with HER2-positive breast cancer, who met the entry criteria, were considered as hypothetic patients of this economic analysis. Their median age was 49, and Japanese and node-negative patients were also included.

Based on the interim analysis of 2-year HERA follow up in 2007 [7], we only compared the economic efficiency for the 1-year of trastuzumab group (initial dose 8 mg/kg, maintenance dose 6 mg/kg, every 3 weeks for 1 year) and the observation group (adjuvant or neoadjuvant chemotherapy only). The hazard ratio for the risk of recurrence in the 1-year trastuzumab group, compared with the observation group, was 0.64 (95% confidence interval: 0.54–0.76; $P < 0.0001$), which was subject to probabilistic sensitivity analysis on the presumption of normal distribution on the log scale.

Major assumption

It is unknown how long the effect of trastuzumab continues, because HERA data cover only a 2-year median follow-up period. To take this uncertainty into account, the cost-effectiveness of trastuzumab was calculated for three hypothetic scenarios, with risk reduction continuing constantly for 2 years (conservative scenario), 5 years (standard scenario), and 10 years (optimistic scenario). After the end of the efficacy period of trastuzumab, the recurrence risk of the trastuzumab group is assumed to be equal to that of the observation group.

The next hypothesis is that trastuzumab is used for metastatic patients who have already been administered trastuzumab as adjuvant therapy. According to an inquiry survey of six Japanese leading hospitals participating in the HERA trial, most clinicians reported that they treated metastatic patients with trastuzumab after using it in an adjuvant setting and continued its combination therapy until a patient no longer responded to 3rd-line chemotherapy.

Patient weight may greatly influence the economic analysis result by determining the dose of trastuzumab. Japanese women, in their 50s, weigh an average of 54 kg. We assumed a patient weight of 50–60 kg (two 150 mg vials and one 60 mg vial) with a sensitivity analysis for patients weighing 50 kg (two 150 mg vials) and 60–75 kg (three 150 mg vials).

The assumed risk of recurrence during the first 5 years is higher than that during the next 5 years. The exact change of recurrence risk is not well defined, particularly not for HER2-positive patients. We presumed the recurrence risk after 5 years to be half that of the previous 5 years, continuing for the patients' lifetime [1]. This parameter was also subject to sensitivity analysis.

Furthermore, trastuzumab-caused cardiac events, which may affect QoL, are thought to be reversible [12, 13]; and thus may not affect life-year.

Markov model and therapeutic strategy

Figure 1(a) shows our constructed Markov model, modeling the therapeutic strategy for metastatic patients recommended by Hortobagyi [14], as both hormone therapy and chemotherapy until 3rd-line, followed by palliative care. This Markov model mainly consists of four parts, "without recurrence," "local recurrence," "metastatic recurrence," and "death," which are split into some parts corresponding to chemotherapy or hormone therapy stage.

Transition rate and model parameters were based on the HERA trial [7], and other published clinical trials [3, 15–19], (Table 1(a)). Transition rate was calculated from percentages of events or median time to progression and is assumed to follow a beta distribution in probabilistic sensitivity analysis. The percentage of cardiotoxicity is 0.6% (severe), 2% (symptomatic), and 3% (asymptomatic) [7]. Although in Fig. 1(a) the arrows of each state to death were not drawn, this transition rate, which is the probability of death due to causes other than breast cancer, is considered to be equal to the natural death rate in Japan.

We also postulated a standard therapeutic strategy corresponding to each Markov state Fig. 1(b), by referring to the Japanese clinical practice guideline for breast cancer and multiple experts' opinions. In Japan, little cost-of-illness data exist; e.g., the treatment cost for

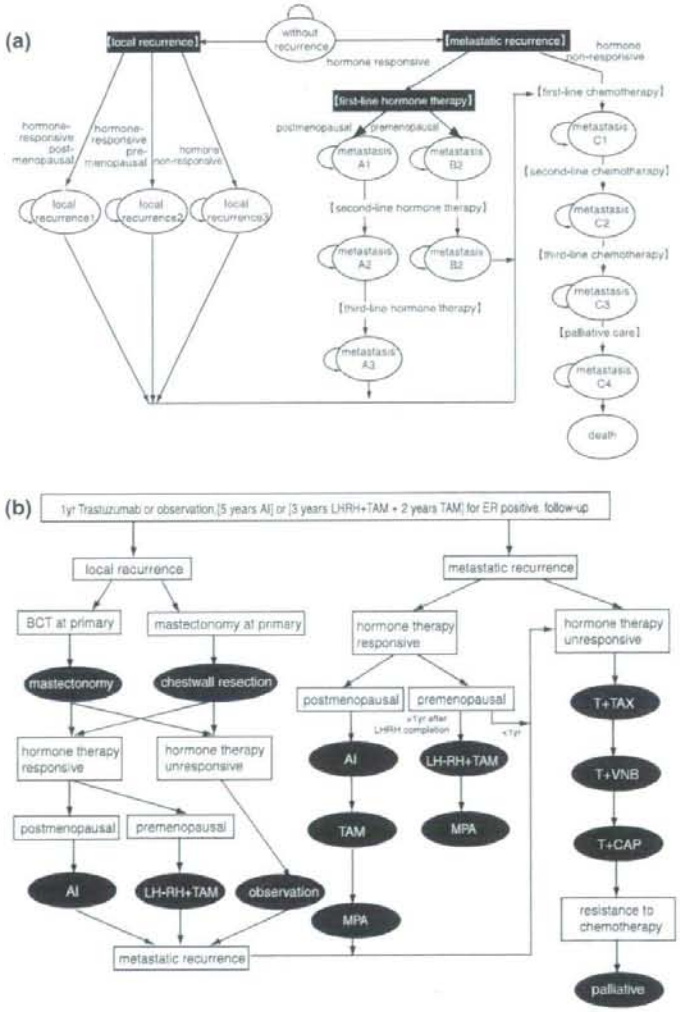

Fig. 1 (**a**) Markov model. All patients start in the "without recurrence." Patients move to an alternative health state with transition probability until they reach "death." Arrows indicate the passages from one state to another. (**b**) Assumed process of breast cancer treatment. The white letters on a dark eclipse background mean concrete treatment. AI: aromatase inhibitor, TAM: tamoxifen, LH-RH: LHRH agonist, MPA: medroxyprogesterone acetate T: trastuzumab, TAX: paclitacel, VNB: vinorelbine, CAP: capecitabine

Table 1 The parameters and costs of each stage

(a) Parameters		
Transition rate		Source
1-year trastuzumab group		
'Without recurrence' to 'metastatic recurrence'	0.004483	7
'Without recurrence' to 'local recurrence'	0.001296	7
Observation group		
'Without recurrence' to 'metastatic recurrence'	0.006916	7
'Without recurrence' to 'local recurrence'	0.001737	7
Both groups (after recurrence)		
'MetastasisA1' to 'metastasisA2' (aromatase inhibitor)	0.07109	13
'MetastasisB1' to 'metastasisB2' (LH-RH agonist plus tamoxifen)	0.07413	14
'MetastasisA2' to 'metastasisA3' (second-line hormone therapy)	0.1091	Experts' opinion
'MetastasisB2' to 'metastasisC1' (second-line hormone therapy)	0.1091	Experts' opinion
'MetastasisA3' to 'metastasisC1' (third-line hormone therapy)	0.1591	Experts' opinion
'MetastasisC1' to 'metastasisC2' (trastuzumab plus taxane)	0.09558	3
'MetastasisC2' to 'metastasisC3' (trastuzumab plus vinorelbine)	0.16674	15
'MetastasisC3' to 'metastasisC4' (trastuzumab plus capecitabine)	0.13191	16
'MetastasisC4' to 'death' (palliative)	0.1091	Experts' opinion
'Local recurrence1–3' to 'metastasis C1'	0.008478	17
Background of patients		
Average age of patients	50	7
Hormone-receptor-positive	0.5	7
Premenopausal	0.85	7
Mastectomy of primary tumor	0.5	7
Cardiotoxicity		
Severe congestive heart failure	0.006	7
Symptomatic congestive heart failure	0.02	7
Asymptomatic congestive heart failure	0.03	7
Major assumption		
The efficacy period of trastuzumab (base-case, years)	5	
Patients weight (kg)	50–60	
Patient age	50	
Risk ratio of recurrence during the next 5 years compared with first 5 years	0.5	
Discount rate	0.03	11

(b) Costs			
	Treatment	Cost (JPY)	Unit
Adjuvant trastuzumab			
Weight = 50–60 kg (first cycle)	Trastuzumab (L.D: 8 mg/kg)	300,000	per month
Weight = 50–60 kg (after second month)	Trastuzumab (6 mg/kg/3 weeks)	280,000	per month
Weight < 50 kg (first cycle)	Trastuzumab (L.D: 8 mg/kg)	250,000	per month
Weight < 50 kg (after second month)	Trastuzumab (6 mg/kg/3 weeks)	240,000	per month
Weight = 60–75 kg (first cycle)	Trastuzumab (L.D: 8 mg/kg)	350,000	per month
Weight = 60–75 kg (after second month)	Trastuzumab (6 mg/kg/3 weeks)	350,000	per month
Without recurrence (until 5 years)			
ER positive and premenopausal patients (until 3 years)	Leuprorelin (3.75 mg/4 weeks), tamoxifen (20 mg/day)	70,000	per month
ER positive and premenopausal patients (after 3 years)	Tamoxifen (20 mg/day)	16,000	per month
ER positive and postmenopausal patients	Anastrozole (1 mg/day)	22,000	per month
ER negative patients	Follow-up[b], annual mammography,	700	per month

Table 1 continued

Without recurrence (after 5 years)			
All patients	Annual follow-up and mammography	400	per month
Local recurrence			
Surgery	Mastectomy or resection	800,000	per event
Local recurrence1 (until 5 years)	Exemestane (25 mg/day)	51,000	per month
Local recurrence2 (until 5 years)	Leuprorelin (3.75 mg/4 weeks), tamoxifen (20 mg/day)	70,000	per month
Local recurrence3 (until 5 years)	Only follow-up	700	per month
All patients (after 5 years)	Annual follow-up and mammography	400	per month
Metastatic recurrence			
MetastasisA1	Exemestane (25 mg/day)	51,000	per month
MetastasisA2	Tamoxifen (20 mg/day)	45,000	per month
MetastasisA3	Medroxyprogesterone (800 mg/day)	77,000	per month
MetastasisB1	Leuprorelin (3.75 mg/4 weeks), tamoxifen (20 mg/day)	70,000	per month
MetastasisB2	Medroxyprogesterone (800 mg/day)	77,000	per month
MetastasisC1 (weight = 50–60 kg, first month)	Trastuzumab (L.D: 4 mg/kg, 2 mg/kg/week), paclitaxel (80 mg/ m^2)	600,000	per month
MetastasisC1 (after second month)	Trastuzumab (2 mg/kg/week), paclitaxel (80 mg/ m^2)	480,000	per month
MetastasisC2 (weight = 50–60 kg)	Trastuzumab (2 mg/kg/week), vinorelbine (25 mg/m^2)	370,000	per month
MetastasisC3 (weight = 50–60 kg)	Trastuzumab (2 mg/kg/week), capecitabine (1200 mg/day)	340,000	per month
MetastasisC4	Palliative care	1,100,000	per event
Bone metastasis	Pamidronate (90 mg/4 weeks)	70,000	per month
Adverse event (cardiotoxicity)			
Severe congestive heart failure		810,000	per event
Symptomatic congestive heart failure		170,000	per event
Asymptomatic congestive heart failure		40,000	per event

[a] We assumed coefficient of variation was 0.4 that was arbitrary value but chosen to give a quite large standard deviation based on A. Briggs. [20]

[b] (1) 4-month intervals for 2 years, (2) 6-month intervals for 2–5 years,(3) annually after 5 years based on the follow up guideline by ASCO [21]

metastatic patients is unknown, so we calculated the sum of each treatment cost in constructing this Markov model and estimated only direct medical costs based on the per piece Japanese drug tariff and reimbursement schedule, (Table 1 (b)). This included the cost of supportive care (anti-emetic agents [22], etc.), heart monitoring, routine follow-up [21], diagnostic imaging, blood tests, and so on. In the probabilistic sensitivity analysis, all cost data were modeled as normal distributions with the base-case value as the mean.

Results

Cost effectiveness result

The cost-effectiveness analysis compared the 1-year trastuzumab group with the observation group (Table 2). The ICER of the standard setting (5 years efficacy and 50–60 kg) was JPY 2,740,000 (€18,000) per LYG. The calculation results of other scenario ICER were JPY 1,920,000 (€13,000) and JPY 1,080,000 (€7,200) per LYG for the period of trastuzumab efficacy, respectively, of 10 years (a somewhat optimistic scenario), and throughout the life time (optimistic scenario).

The ICER becomes higher, however, with increased patient weight. At the 60–75 kg weight class, which is heavier than the standard class, the ICER changed from JPY 2,300,000 (€15,000) to JPY 7,400,000 (€49,000) for differing trastuzumab efficacy periods (5 to 50 years) and at 50–60 kg, which is a lighter class, ranged from JPY 1,500,000 (€10,000) to JPY 5,100,000 (€34,000).

Sensitivity analysis

The most influential parameter was the period of trastuzumab efficacy. The results are shown in Fig. 2 for every weight class; and when trastuzumab efficacy continues for more than 2 years, the ICER was less than JPY 7,500,000 (€50,000) for any weight class. Other one-way sensitivity analyses for parameters (discount rate, recurrence rate, cardiotoxicity costs, and terminal costs), showed little change. Among them, however, the discount rate was the most influential parameter, and all the results of sensitivity

Table 2 The result of cost-effectiveness analysis and sensitivity analysis

(a) The result of cost-effectivess analysis (weight = 60 kg)

	C	E	ΔC/ΔE (ICER)	
Observation	¥7,900,000	12.46		
Trastuzumab (conservative)	¥11,500,000	13.06	¥6,000,000	€40,000
Trastuzumab (standard)	¥11,200,000	13.70	¥2,600,000	€17,000
Trastuzumab (optimistic)	¥10,900,000	14.10	¥1,800,000	€12,000

(b) The relationship between weight class and efficacy period of trastuzumab

		Weight class		
Efficacy period of trastuzumab		less than 50 kg	50–60 kg	60–75 kg
	2 years	¥5,100,000	¥6,000,000	¥7,400,000
	(Conservative)	€34,000	€40,000	€49,000
	5 years	¥2,200,000	¥2,600,000	¥3,300,000
	(Standard)	€15,000	€17,000	€22,000
	10 years	¥1,500,000	¥1,800,000	¥2,300,000
	(Optimistic)	€10,000	€12,000	€15,000

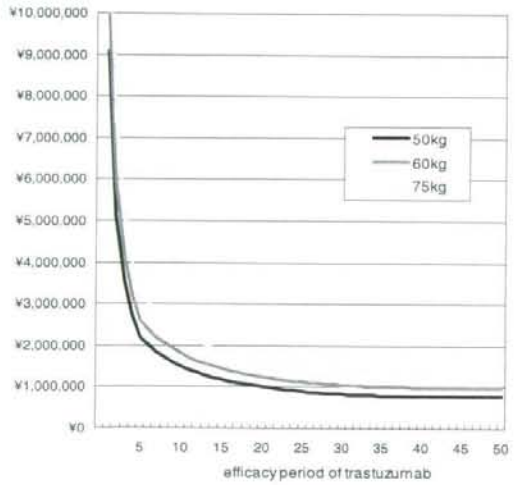

Fig. 2 Uncertainty of cost-effectiveness analysis. The relation between ICER and efficacy period of trastuzumab by weight class

analyses in the standard scenario were less than JPY 5,000,000 (€33,000).

The ICER was changed to ¥4,700,000 (€31,000), ¥1,900,000 (€14,000), and ¥1,300,000 (€9,000) per LYG for the period of trastuzumab efficacy, respectively, of 2, 5, and the10 years, based on the 1-year follow-up data [6].

The acceptability curve of the standard setting is shown in Fig. 3(a), and the probability that the ICER of 1-year trastuzumab was less than JPY 5,400,000 (€36,000) was above 95%. Figure 3(b) shows the incremental cost-effectiveness plane and the 5 percentile and 95 percentile for incremental LYG were estimated to be 0.77 and 1.65. The 5 percentile and 95 percentile for incremental costs were JPY 900,000 (€15,000) and JPY 5,550,000 (€28,000).

Discussion

In Japan, as with other developed countries, the serious social problem of burgeoning medical costs, caused by rapid aging and the evolution of healthcare technology prompts us to consider the efficiency of new expensive healthcare technology.

For metastatic patients, the trastuzumab ICER was estimated as £19,000 (monotherapy) and £37,500 (combination) by NICE, which recommended both trastuzumab monotherapy and combination therapy based on this economic evaluation [23]. Furthermore, NICE issued the guidance recommending trastuzumab as a treatment option based on the 1-year follow-up data of the HERA trial [10]. They estimated that the ICER of 1-year trastuzumab was £18,000 per additional QALY ranging from £16,000 to £33,000.

NICE suggests that the ICER threshold should be £20,000 to £30,000 (=JPY 5,000,000–JPY 7,000,000) per QALY. In the US, $50,000 or $100,000 per QALY is often used as the threshold. In Japan, no cost effectiveness threshold for treatment has been determined; however, it is thought that the values of the NICE's thresholds are acceptable, because of the similar economic and medical environments in UK and Japan.

In US trials, weekly adjuvant trastuzumab therapy had an ICER of US$ 18,970 per QALY [24] and US$ 39,982 per QALY [25] estimating from the joint analysis (NSABP B-31 and NCCTG N9831 trials) [8]. Both papers also conclude that adjuvant trastuzumab is cost-effective. It confirms that

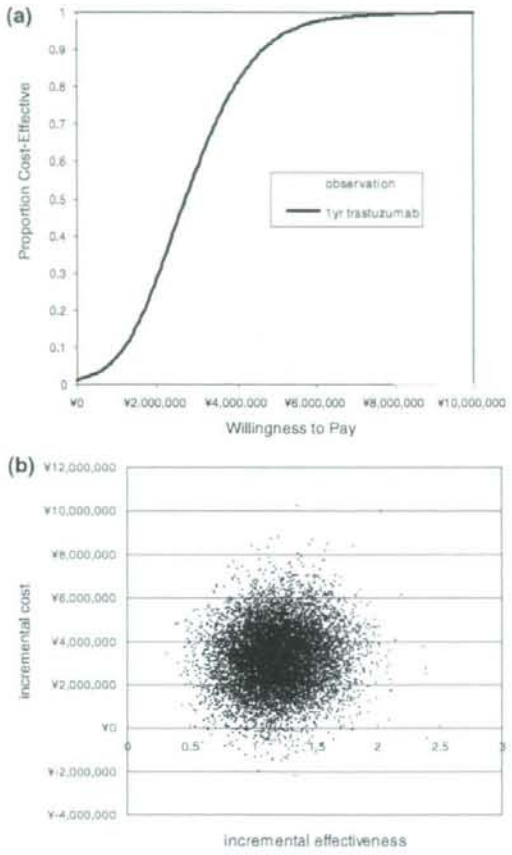

Fig. 3 (**a**) Acceptability curve for 1-year trastuzumab versus observation in a standard setting (5 years of efficacy and 50–60 kg) simulated 10,000 times (**b**) Incremental cost-effectiveness plane for trastuzumab versus observation alone

the conclusion is consistent between the HERA trial and the joint analysis-based economic evaluation.

We calculated the ICER based on the 2-year follow-up data of the HERA trial in this analysis, although other cost-effectiveness analyses of trastuzumab were based on 1-year follow-up data. We had difficulty showing the exact ICER value and predicting the long-term prognosis for the trastuzumab patients' group, which greatly influences the result of this economic evaluation. The results of other large trials, B31/N9831, show that the hazard ratio in the third or fourth year is nearly equal to that in the first year [8]. It is natural to assume that the efficacy of the HERA regimen continues for at least an equivalent period. Thus, we think the base case is 5 years. However, when trastuzumab efficacy continues at least for more than 2 years, which is a conservative setting, the ICER is less than JPY 7,500,000 (€50,000) for any weight class. There is little difference between LYG and QALY in oncology [26], so we could conclude that the 1-year trastuzumab treatment is cost-effective from this analysis, even based on 2-year follow-up data.

The limitation of this result is that our endpoint is LYG not QALY, because in Japan there are no HRQoL data for breast cancer patients applied to our analysis, and we decided it was better to use LYG than the QALY calculated by foreign, not Japanese utility values. In addition, the transition rates derived from published data and costs were calculated by the construction of a standard therapy model, not analyzed by using patient-level data.

In this analysis we adopted the health-care payers' perspective. When the perspective was changed to a societal one, the indirect costs of the trastuzumab group were higher than those of the control group in the first yearly period of trastuzumab therapy. But considering that the expected value of incremental effectiveness is more than 1 year, the indirect costs of the trastuzumab group were lower, as a whole.

It is important to analyze not only the cost-effectiveness but also the budget impact. We considered the incremental cost of 1-year trastuzumab treatment as JPY 2,000,000–4,000,000 (€13,000–26,000) from Table 2. Then, by estimating the number of new breast cancer patients per year to be 40,000, of which 20% are HER2-positive, the total incremental cost was JPY 16–32 billion (€105–210 million), if all the HER2-positive patients were treated by trastuzumab.

In the Finland Herceptin (FinHer) trial [27], 9 weeks of trastuzumab injections yielded a hazard ratio equivalent to that of other studies in which trastuzumab was administered for 1 year. We cannot conclude that 9 weeks of injections is optimal from the FinHer trial, because it included fewer patients ($N = 232$). But this RCT showed a noteworthy result. If the efficacy of 9 weeks of injections is nearly equal to that of 1-year injections, 9-week treatment would be more cost-effective as well as provide greater patient convenience. However, the optimal period of adjuvant trastuzumab treatment has not yet been decided. At present, in the HERA trial, the comparison of 1-year and 2-year treatments has not been demonstrated. When they are available, the cost-effectiveness analyses will play an important role in determining the optimized treatment period.

The price of trastuzumab (¥78,074 (€520) per 150 mg vial) in Japan is lower than that in the UK (£407.40 (€650) per 150 mg vial), which is less than that in other developed countries. At the same time, the Japanese women's average weight is less than that of westerners, and they have the highest life expectancy rates in the world. Though NICE

estimated the average cost per person as £24,600 (JPY 5,900,000) in the UK [10], our calculated cost is JPY 3,390,000 (£14,000) in the standard setting. The Japanese women have an advantage over westerners in cost-effectiveness of adjuvant trastuzumab administration.

Based on the results of some RCTs and our economic analysis, we can conclude that the 1-year trastuzumab adjuvant treatment is superior to observation only in terms of the cost-effectiveness.

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A Questionnaire Survey of Physicians' Perspectives Regarding the Assessment of Chemotherapy-induced Peripheral Neuropathy in Patients with Breast Cancer

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Objective: Since there is now growing interest in the incorporation of patient-reported outcome measures in cancer clinical trials, a patient-based questionnaire, the Patient Neurotoxicity Questionnaire (PNQ) was developed to quantify the symptoms and severity of chemotherapy-induced peripheral neuropathy (CIPN). The aim of this study was to evaluate the physicians' perspectives regarding the utility and diagnostic value of PNQ.
Methods: A questionnaire was sent to 61 physicians who participated in a Phase III randomized trial of adjuvant chemotherapy in breast cancer (AC followed by taxane versus taxane alone) that used the PNQ to assess CIPN.
Results: Forty-seven out of 61 physicians (77%) responded. The majority considered neurosensory symptoms the diagnostic hallmark for CIPN and most regarded interference with activities of daily living (ADLs) as definite justification for treatment modifications. For neurosensory disturbance, the majority of physicians indicated that Grade D severity (moderate to severe symptoms interfering with ADLs) should result in treatment postponement and Grade E severity (severe symptoms preventing most ADLs) should result in treatment discontinuation. Similarly, for neuromotor disturbance, over half of the physicians replied that Grade C (moderate symptoms not interfering with ADLs), D and E severity should result in dose reduction, treatment postponement and treatment discontinuation, respectively. Eighty-four percentage of the physicians reported that the use of the PNQ was helpful in the diagnosis and assessment of patients at risk of CIPN.
Conclusions: The PNQ appears to be a useful instrument for the diagnosis and grading of CIPN, as well as for clinical decision-making regarding treatment modifications secondary to CIPN.

Key words: neuropathy – chemotherapy – patient-reported outcome – questionnaire – breast cancer

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and serious clinical problem that affects many patients receiving chemotherapy with agents such as platinum compounds, taxanes and vinca alkaloids (1–3). Besides compromising a patient's quality of life (QOL), it can result in chemotherapy dose reduction, treatment postponement or treatment discontinuation, as no standard therapy exists for the prevention and treatment of CIPN (2–4). Until now, physician-based instruments such as the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) or the World Health

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Organization (WHO) classification have been most widely used to assess CIPN (2,5–7). However, the symptoms and severity of CIPN are largely subjective in nature, so that diagnosis and grading are not always straightforward. Furthermore, the absence of a universally recognized standard for quantifying CIPN symptoms makes comparisons among published studies of CIPN difficult. More importantly, current evidence suggests that physician-based assessments under-report the incidence and severity of CIPN (8–10). Therefore, the development of a new and reliable method for the assessment of CIPN would represent an important medical advancement not only for cancer patients but also for health-care providers involved in its diagnosis and management.

Given the foregoing, there is now growing interest in the incorporation of patient-reported outcome (PRO) measures in cancer clinical trials (11), and recently a patient-based questionnaire, the Patient Neurotoxicity Questionnaire (PNQ) was developed to quantify the symptoms and severity of CIPN (2). A Phase III randomized trial of adjuvant chemotherapy in breast cancer, the National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 02 (AC followed by taxane versus taxane alone), demonstrated that the PNQ is a reliable, sensitive and responsive instrument for assessing CIPN (9,12,13). In this survey, we aimed to obtain and evaluate the perspectives of the physicians who participated in the study mentioned, regarding their experience with the PNQ in Japan, using a questionnaire.

PATIENTS AND METHODS

Patient Neurotoxicity Questionnaire

The PNQ is a simple self-administered instrument designed and developed by BioNumerik Pharmaceuticals, Inc. with input from the US Food and Drug Administration (FDA). It comprises specific questions designed to obtain clinically relevant and quantifiable CIPN diagnostic information directly from the patient, regarding the incidence and severity of subjective CIPN symptoms (e.g. tingling, pain and numbness) (2) (Table 1). It is also designed to make a clear delineation between no interference and interference with defined activities of daily living (ADLs). This demarcation falls between Grades C and D, and corresponds to the absence (Grade C or less) or presence (Grade D or higher) of neurosensory or neuromotor symptoms that interfere with ADLs. In addition, patients with Grades D or E are asked to identify which activity or activities are interfered with as a result of therapy.

A Japanese translation (from the original English) has been developed using forward and backward translation with review by several oncologists, neurologists and linguistic experts who are fluent in both English and Japanese (9).

Survey Questionnaire

The questionnaire (available from the Comprehensive Support Project for Oncology Research, CSPOR and Comprehensive Support Project for Health Outcomes Research, CSP-HOR, http://www.csp.or.jp/) was developed through discussions with an expert panel that included experienced breast oncologists and social scientists. First, each respondent was asked to check or otherwise indicate all specific patient-reported symptoms that he/she, as a clinician, believed were conclusive for the diagnosis of CIPN. These symptoms included numbness, tingling, burning pain, pain, discomfort, pins and needles. The respondents were then asked to identify the patient-reported PNQ grade and physician-reported NCI-CTCAE grade that would lead them to a decision to continue, postpone, discontinue or modify the dose of chemotherapy. They were also asked whether they considered Grade C neurotoxicity clinically significant, whether the PNQ would be helpful in the management of patients at risk of CIPN, and whether the list of ADLs located in the bottom portion of the PNQ was adequate. Finally, the characteristics of the respondents were assessed by 11 questions about age, gender, specialty, board certification, clinical experience as a breast oncologist, number of breast cancer patients diagnosed in the hospital per year,

Table 1. Patient neurotoxicity questionnaire

	A	B	C	D	E
Item 1	I have no numbness, pain, or tingling in my hands or feet.	I have mild tingling, pain or numbness in my hands or feet. This does not interfere with my activities.	I have moderate tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate to severe tingling, pain or numbness in my hands or feet. This interferes with my activities of daily living.	I have severe tingling, pain or numbness in my hands or feet. It completely prevents me from doing most activities.
Item 2	I have no weakness in my arms or legs.	I have mild weakness in my arms or legs. This does not interfere with my activities.	I have moderate weakness in my arms or legs. This does not interfere of my activities of daily living.	I have moderate to severe weakness in my arms or legs. This interferes with my activities of daily living.	I have severe weakness in my arms or legs. It completely prevents me from doing most activities.

Additional information on specific activities of daily living that were affected in patients answering D or E: Button clothes, use a spoon, use a knife, use a fork, other eating utensils, open doors, put in or remove contact lenses, dial or use a touch tone telephones, operate a remote control, fasten buckles, sleep, climb stairs, type on a keyboard, write, walk, put on jewelry, knit, sew, work, tie shoes, drive. The patient was requested to specify in the space, if activities of importance to her/him have been interfered as a result of therapy.

clinical experience of CIPN, clinical experience of neurological disorders other than CIPN, availability of an on-site neurologist, the cooperative framework of the neurologist and confidence with CIPN management.

Participants

We selected 61 higher acerues who participated and actually treated patients in N-SAS BC 02 as potential respondents. The endpoints of N-SAS BC 02 included the prospective assessment of health-related QOL as well as validation of the PNQ in breast cancer patients receiving neurotoxic and non-neurotoxic treatment (9,12,13). The assessment was made at baseline, 3, 5, 7 and 12 months after starting adjuvant chemotherapy in the first 300 patients enrolled, and the instruments were directly sent to CSPOR data center by the patient without checking by her physician and nurses. The clinical research coordinator could check the omission of recording, however, the result of these assessments was kept from the physician. In N-SAS BC 02, the questionnaire completion rate was more than 90% at any assessment point (12,13).

In June 2006, the questionnaire was mailed with a covering letter explaining that this survey was confidential and anonymous. Consent to participate was indicated by the completion and return of the questionnaire. A second survey was mailed to physicians who had not returned the questionnaire within 2 weeks of the initial mailing. This study was performed according to the ethical guidelines for epidemiological research (http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/sisin2.html).

Data Analysis

The chi-squared test, Fisher's exact test and the Kruskal–Wallis test were performed using JMP7, and P values less than 0.05 were considered statistically significant.

RESULTS

Survey Participants

Forty-seven of the 61 physicians (77%) responded (36% at first survey, 64% after second survey) (Table 2). The median age of the respondents was 47 years (range, 34–66). The majority was surgeons working at a cancer center or core hospital and was also experienced breast oncologists. The median duration of experience in breast oncology was 15 years (more than 10 years in 53% of respondents), and 67% were specialists certified by the Japanese Breast Cancer Society. All physicians had experience in the diagnosis and management of CIPN, and half of them had experience with peripheral neuropathy of differing etiologies. There was no full-time neurologist in 61% of the hospitals, and 91% of physicians felt insecure about the diagnosis and management of CIPN.

Answers Regarding Symptoms of CIPN

As shown in Fig. 1, numbness (100%), tingling (74%), pain (58%) and weakness (65%) were rated as symptoms conclusive for the diagnosis of CIPN by the majority of physicians. Other symptoms such as burning (39%), discomfort (22%) and pins and needles (30%) were considered less significant. The majority of physicians selected numbness (61%),

Table 2. Responders' characteristics

	No.	%
Age, years (mean)	46 (34–66)	
Sex		
M/F	44/3	94/6
Breast oncology experience, years (mean)	15 (2–30)	
Practice setting		
Cancer center/general/university	22/18/7	47/38/15
Specialty		
Surgery/internal medicine/others	39/4/4	82/9/9
Board certification by Japanese Breast Cancer Society		
Yes/no	31/16	66/34
Experience of CIPN[a]		
Yes/none	44/0	100/0
Experience of PN by the other cause[a]		
Yes/none	22/22	50/50
Availability of on-site neurologist[b]		
Yes/no	18/27	39/61
Diagnosis and management of CIPN[b]		
Confident/Insecure	4/41	9/91

CIPN, chemotherapy-induced peripheral neuropathy; PN, peripheral neuropathy; M/F, male/female.
[a,b]Three or two responders with missing data were not evaluable, respectively.

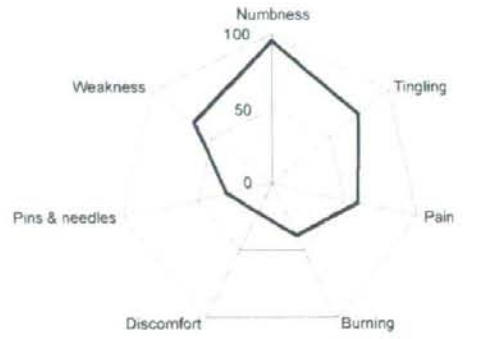

Figure 1. Symptoms considered conclusive for a diagnosis of chemotherapy-induced peripheral neuropathy (CIPN) ($n = 46$). Respondents were able to choose more than one answer.

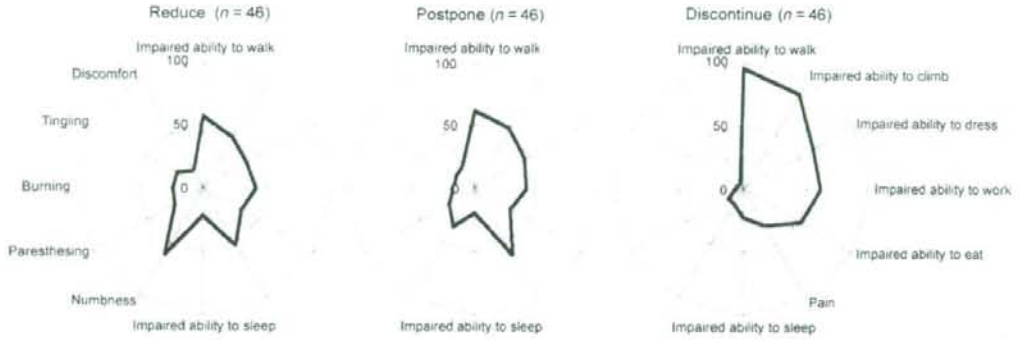

Figure 2. Treatment decisions according to qualitative symptoms of CIPN. Respondents were able to choose more than one answer. Reduce, continue treatment, however, reduce the chemotherapy dose level; Postpone, postpone treatment until the patient's symptoms improve; Discontinue, discontinue treatment.

impaired ability to walk (57%) or pain (52%) as reasons for a dose reduction (Fig. 2). Similarly, the majority of physicians indicated that they would postpone chemotherapy if patients had impaired ability to walk (61%), pain (61%) or impaired ability to climb stairs (54%). As reasons for treatment discontinuation, almost all selected impaired ability to walk (96%) and climb stairs (87%); and the majority of physicians selected impaired ability to dress (63%), work (61%) or eat (52%).

Decisions Regarding Treatment Modifications According to the Severity of CIPN

When asked about the treatment modifications according to the PNQ grade for neurosensory or neuromotor disturbance, no physician considered continuation of treatment without modification acceptable at Grade D or E (Figs 3 and 4). For neurosensory disturbance, opinions as to when to reduce the dose were divided between Grades C (42%) and D (44%), while the majority of physicians indicated that Grade D severity should result in treatment postponement (62%) and Grade E severity should result in treatment discontinuation (73%). Similarly, for neuromotor disturbance, over half of the physicians replied that Grades C (54%), D (57%) and E (57%) severity should result in dose reduction, treatment postponement and treatment discontinuation, respectively. These results were not significantly affected by board certification or by duration of breast oncology experience, except for discontinuing of treatment by severity of neuromotor disturbance. When the correlation between the PNQ grade of neuromotor disturbance and the decision to discontinue treatment was analyzed in terms of duration of oncology experience, a significantly higher proportion of physicians who had more than 10 years experience in breast oncology selected Grade E compared with those who had less experience in breast oncology (Grades C, D and E: 4, 25 and 70% among the former; 0, 63 and 37% among the latter, respectively, $P < 0.05$).

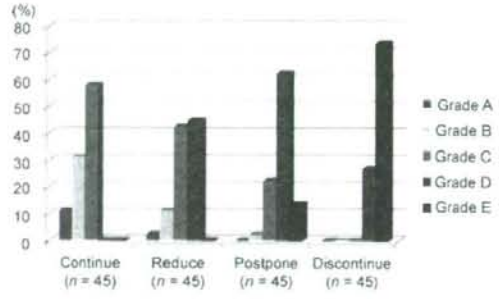

Figure 3. Treatment decisions according to Patient Neurotoxicity Questionnaire grades for neurosensory symptoms. The highest grade leading to a decision to continue and the lowest grade leading to a decision to reduce the dose or to postpone or discontinue treatment was recorded where multiple responses were obtained. Continue, continue treatment without postponement or modification of the chemotherapy dose level; Reduce, continue treatment, however, reduce the chemotherapy dose level; Postpone, postpone treatment until the patient's symptoms improve; Discontinue, discontinue treatment.

Regarding NCI-CTCAE grades, all physicians considered it appropriate to continue treatment if the severity of sensory or motor neuropathy was Grade 1, and none opted to discontinue treatment when the severity of sensory or motor neuropathy was Grade 1, or 2 (Fig. 5). When the severity of sensory or motor neuropathy was Grade 3, 57% of physicians chose to postpone treatment, and when it was Grade 4, the majority selected to discontinue treatment (87% in sensory neuropathy and 91% in motor neuropathy). These results were not significantly affected by board certification, or by duration of breast oncology experience (data not shown).

Physicians' Perceptions Regarding the PNQ

Regarding the utility of the PNQ, 42% of physicians considered Grade C as clinically significant, 84% of physicians rated the PNQ as helpful in management of patients at risk of CIPN and 93% considered the list of ADLs sufficient. In addition, some of respondents indicated that Grade C would predict the occurrence of more severe CIPN.

DISCUSSION

This survey demonstrated that a large proportion of physicians were not confident about the diagnosis and management of CIPN, despite the fact that the majority of them was specialist breast oncologists, and all had experience in the diagnosis and management of CIPN. This might be associated not only with the absence of support by on-site neurologists in many cases, but also with the lack of standardized assessment methods for CIPN.

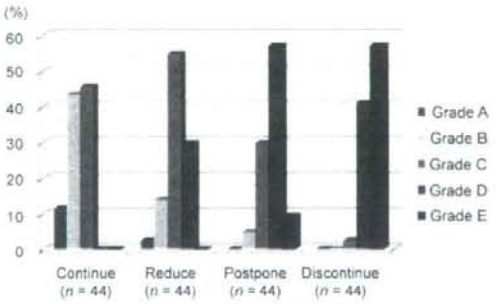

Figure 4. Treatment decisions according to PNQ grades for neuromotor symptoms. The highest grade leading to a decision to continue and the lowest grade leading to a decision to reduce the dose or to postpone or discontinue treatment was recorded where multiple responses were obtained. Continue, continue treatment without postponement or modification of the chemotherapy dose level; Reduce, continue treatment, however, reduce the chemotherapy dose level; Postpone, postpone treatment until the patient's symptoms improve; Discontinue, discontinue treatment.

In general, the most common features of CIPN are predominantly sensory distal neuropathic symptoms, including a mixture of paresthesia and dysesthesia, and complaints described as burning, numbness, tingling and shooting pains, typically in a glove-and-stocking distribution. Motor neuropathy is not well recognized and is believed to be much less common than sensory neuropathy (1,14). The majority of physicians involved in this survey considered neurosensory symptoms to be the diagnostic hallmark for CIPN. In addition, decisions in favor of dose reduction, treatment postponement or treatment discontinuation were predominantly due to the presence of impaired ability to perform ADLs such as walking, climbing stairs, dressing, working and eating. These results support the appropriateness of using interference with ADLs as the demarcation between PNQ Grades C and D, and demonstrate the important role a patient-based instrument can play in the diagnosis and assessment of the severity of CIPN as well as in treatment decision-making.

Until now, one of the most widely recognized physician-based approaches used to assess CIPN has been the NCI-CTCAE (2,10,15). However, this approach requires both patient cooperation and skill on the part of physicians to obtain essential diagnostic information regarding CIPN. From the viewpoint of the treating physician, the grading scheme should be clinically meaningful, and sufficiently sensitive, specific and reliable to detect CIPN. In this survey, all physicians chose to continue treatment with or without dose modification if the PNQ grade was Grade C or lower, i.e. if neurosensory or neuromotor symptoms did not interfere

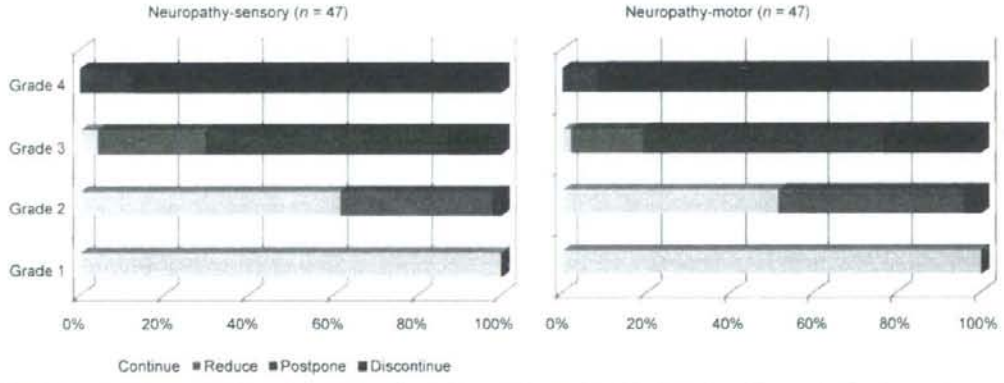

Figure 5. Treatment decisions according to National Cancer Institute's Common Terminology Criteria for Adverse Events grades. Continue, continue treatment without postponement or modification of the chemotherapy dose level; Reduce, continue treatment, however, reduce the chemotherapy dose level; Postpone, postpone treatment until the patient's symptoms improve; Discontinue, discontinue treatment.

with ADLs. In contrast, they selected treatment modifications such as reducing the dose, or postponing or discontinuing treatment, if the patient's PNQ score was Grade D or E; the grades correspond to the presence of neurosensory or neuromotor symptoms that interfere with ADLs, or that completely prevent ADLs, respectively. It is also important to note that decision-making regarding treatment modifications by PNQ grade was not affected by board certification or duration of breast oncology experience, barring one exception. In this survey, the decision to discontinue treatment due to neuromotor disturbance varied by duration of breast oncology experience. Although we could not determine whether this was due to the experience level itself or other factors, these results agree with the main purpose behind the development of the PNQ, which was designed to allow adequate assessment of both the severity of symptoms and the degree of functional impairment in patients at risk of CIPN. In this respect, the PNQ appears to be suitable for use in decision-making regarding treatment postponement, dose modification and treatment discontinuation.

In the questions regarding making decisions about treatment modifications based on NCI-CTCAE grading, the results were similar to those obtained with the PNQ. Most physicians chose to postpone or discontinue treatment if sensory or motor neuropathy was Grade 3, and the great majority of them selected to discontinue treatment if the severity was Grade 4. The NCI-CTCAE neuropathy categories range from Grade 0 (which includes the normal range) to Grade 5 (death), where Grade 4 means life-threatening or disabling. It is important to note, however, that no specific ADLs are defined in the NCI-CTCAE grading, and the diagnostic criterion of 'interfering with function, but not interfering with ADLs' is ambiguous and may be interpreted inconsistently by physicians (2). Moreover, the specific activities and levels of function that are compromised are neither defined nor captured as part of the NCI-CTCAE grading system. Interestingly, when several grading scales for the assessment of CIPN were compared by Postma et al. (5), interobserver agreement for the National Cancer Institute of Canada-Common Toxicity Criteria (NCIC-CTC) was the lowest. These investigators compared four different grading scales (the NCIC-CTC, Eastern Cooperative Oncology Group, WHO and Ajani scales), and found disagreement between two neurologists on at least one of these scales in 80% of the patient evaluations (i.e. complete agreement on all grades of all scales was noted in only 20% of patients). The overall percentage of interobserver agreement on all CIPN grades ranged from 46 to 84%. Moreover, exact agreement on severe (Grade 3) neuropathy using the NCIC-CTC was only 42%, indicating that the evaluation criteria and scoring are not interpreted in the same manner by different examiners. The variability in determining CIPN grades using these scales indicates that physician-based instruments can lead to ambiguities when deciding upon treatment modifications. NCIC-CTC is a grading scale similar to NCI-CTCAE, and thus, NCI-CTCAE may be subject to the same variability and resulting disadvantages.

The other available patient-based questionnaires might include Functional Assessment of Cancer Therapy (FACT)-Taxane, FACT&GOG-Ntx (16,17). These instruments are more discerning but contain questions that are not specific for the assessment of CIPN. Moreover, they report an overall numerical score that is the sum of several subscores, including neurosensory, neuromotor and autonomic symptoms, and do not define the demarcation or scoring of clinically important functional impairment of ADLs (2). In addition, no medical interpretation of functional impairment of ADLs is provided by these instruments. Importantly, CIPN assessment should be practical and convenient for both patients and health-care providers, and should not require any invasive procedures or large amounts of time and resources to perform (2,3,15). In this respect, the PNQ with its defined list of ADLs appears to fulfill these criteria. It also appears to be acceptable to health-care providers, as most of the physicians involved in this survey considered it helpful in the management of patients at risk of CIPN. In addition, the breakpoint between Grades C and D, in other words, the absence or presence of interference with ADLs, was considered to be significant from the viewpoint of physicians treating patients at risk of CIPN. However, further studies will be needed to address the question of whether PNQ Grade C can predict the occurrence of more severe CIPN.

CONCLUSION

It is currently not standard practice in routine cancer care or clinical trials to directly collect PROs including symptoms of CIPN, or to use these data as a basis for clinical decision-making, research conclusions or drug approval. However, the PNQ appears to be a useful instrument with high acceptability by physicians, not only for collecting information about the symptoms and severity of CIPN, but also in making decision regarding treatment modifications.

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Conflict of interest statement

The author, Frederick H. Hausheer, is the Chairman & Chief Executive Officer, a substantial shareholder and a holder of

stock options of BioNumerik Pharmaceuticals, Inc. The author, Stacey Bain, is an officer and a holder of stock options of BioNumerik Pharmaceuticals, Inc.

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医療連携

がん診療における一般内科医の役割

江﨑 泰斗・政 幸一郎・有山 寛

ポイント

- 外来化学療法の普及に伴い，在宅で過ごす患者の副作用への対応は，治療継続，QOLの維持向上にとって重要である．
- 抗がん薬の催吐作用の程度，嘔気・嘔吐の分類により適切に制吐薬を使用する．
- 経口摂取不良，激しい下痢，発熱性好中球減少の場合は速やかにがん専門医と連携をとる．

国民の2人に1人ががんに罹患し，3人に1人はがんで死亡する時代となり，一般内科医が，がん診療において果たすべき役割は大きい．本稿では一般内科医ががん専門医・専門病院で治療中の患者の診療を依頼されたときの対応について記載する．

外来化学療法の普及

近年，有効性が高く副作用の軽微な抗がん薬の開発，支持療法の進歩，適切な薬物療法の重要性・有用性の認識，QOLを求める考え方の普及，在院日数短縮，外来化学療法加算，包括医療の導入など，がん治療を取り巻くさまざまな状況の変化を背景とし，外来化学療法が注目され普及している．乳癌におけるAC療法(ドキソルビシン，シクロフォスファミド)，パクリタキセル，ドセタキセル，大腸癌に対するFOLFOX療法(5 FU，オキサリプラチン，1-ロイコボリン)，FOLFIRI療法(5 FU，イリノテカン，1-ロイコボリン)，胃癌におけるTS-1，膵癌に対するゲムシタビンなど，多くの固形癌の標準治療が外来通院で施行される．悪性リンパ腫に対するCHOP療法(シクロフォスファミド，ドキソルビシン，ビンクリスチン，プレドニゾロン)，卵巣癌に対するTC療法(パクリタキセル，カルボプラチン)などもしばしば外来で施行される．

患者は，がん専門医の外来を定期的(多くは1～2週ごと)に受診する．当日，採血，診察の結果，化学療法の実施が可能と判断された後，外来化学療法室で1～2時間の点滴治療を受け帰宅する．多くの患者は抗がん薬治療の期間中，外来化学療法室で点滴を行っている急性期の間を除き，ほとんどの時間を在宅で過ごす．新規抗がん薬や制吐薬の進歩があるとはいえ，さまざまな副作用が起こりうる．

がん専門医は患者・家族に，特に在宅で起こりうる症状とその対処法について十分説明し指導している．しかし，がん専門病院では，遠方からの通院治療者，仕事を続けながらの治療者，高齢者などが多く含まれ，これらの患者が

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プライマリケアを担う一般病院や診療所を訪れ，副作用への支持療法を受ける場合は多い．以下，外来化学療法時の副作用，特に消化器毒性，骨髄抑制への対応について記載する．

抗がん薬による消化器毒性への対応

がん化学療法施行中の患者にとって，最もつらいと感じる自覚症状は嘔気・嘔吐，食欲不振，下痢，口内炎などの消化器症状であり，治療の継続にはその対策が欠かせない．

■ 嘔気・嘔吐

嘔吐は急性，遅発性，予測性に分類され対処される．

急性嘔吐は抗がん薬投与後24時間以内に生じ，最も強い．遅発性嘔吐は24時間以降2～5日続く．米国臨床腫瘍学会では抗がん薬を催吐作用の強さにより高度，中等度，低度，最小の4段階に分け，薬剤に応じて制吐薬の予防投与を行うことを推奨している[2]．外来で使用される薬剤の多くは中等度催吐性以下であり，急性嘔吐予防に5 HT_3受容体拮抗薬とデキサメタゾンおよびaprepitant(本邦未承認)の併用，遅延性嘔吐予防に5 HT_3受容体拮抗薬またはデキサメタゾンとaprepitantの併用が推奨されている．具体的には，5 HT_3受容体拮抗薬とデキサメタゾン(4～8 mg)を内服で2～5日間程度投与する．特にデキサメタゾンの投与量はしばしば不十分である．予測性嘔吐は以前の化学療法で強い嘔吐を経験した患者や，治療に対する不安の強い場合にみられる．ロラゼパム0.5 mg，1日3～4回を数日間試みる．

一般内科医が診る治療開始後数日を経た嘔気は，メトクロプラミドやドンペリドンなど通常の制吐薬で軽減できる例も多いが，水分摂取も困難となるような強い嘔気・嘔吐の場合には500～1,000 m*l*程度の輸液を行い経過を見て，改善傾向がなければ速やかにがん専門医と連携をとる．

日常生活において嘔気・嘔吐を和らげる方法の指導が有用である．嘔気時は氷片を口に含む，冷水でのうがい，冷えたレモン水や炭酸飲料などもよい．室内の換気を頻回にし，匂いの強いもの(花，香水，食べ物)は置かない．音楽やテレビなど気分転換の方法も指導する．

化学療法中のがん患者の嘔気・嘔吐のすべてが抗がん薬に起因するものではない．脳転移，腸閉塞，電解質異常(高カルシウム血症，低ナトリウム血症)，オピオイドなどの薬物副作用，あるいは感染性の胃腸炎，心疾患，消化管出血なども十分に念頭に置き検索を行う．

■ 下痢

下痢はイリノテカン，フッ化ピリミジン系薬剤(5 FU，TS-1，UFT，カペシタビンなど)，ドセタキセル，パクリタキセルなどできたすことがあり，その対策は重要である．特に脱水，電解質異常に加え，障害された腸粘膜に白血球減少時の感染を伴うと重篤化し生命を脅かす．

下痢はコリン作動性の早発性のもの(投与24時間以内に発現)と腸粘膜障害による遅発性(24時間以降から6日まで)のものがあり，対策が異なる．早発性の下痢は抗コリン薬(臭化プチルスコポラミンなど)で容易に対応できる．

在宅で対応することになる遅発性の下痢に対してはタンニン酸アルブミン，ケイ酸アルミニウム，塩酸ロペラミド，リン酸コデインなどが有効である．イリノテカンによる遅発性の下痢に対してロペラミド大量投与(塩酸ロペラミド2 mgを2時間ごとに12時間後まで経口投与)が有効といわれるが，軽快しない場合は速やかに医療機関を受診させる．絶食，輸液管理を必要とする場合もあり，がん専門病院と連携する．食物繊維や脂肪の多い食品を避ける，十分な水