Table 3 continued

	I take into account whether she has a spouse/partner when I discuss fertility issues with my patients				I take into account economical status of the patient when I discuss fertility issues with my patients				I discuss fertility issues with breast cancer patients with high risk of recurrence			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.839				0.609				0.910			
Not fair												
Attitude												
Conservative	0.601				0.694				0.001	1.000		
Aggressive										1.640	1.250	2.150
Gender												
Female	0.033	1.089	1.002	1.185	0.622				0.047	1.089	1.000	1.185
Male										1.000		
Age												
<50	0.326				0.267				0.003	1.391	1.131	1.712
>50												
Specialty												
Surgery	0.225				0.343				0.273			
Others												
Affiliation												
University hospital/cancer center	0.364				1.000				0.219			
General hospital/private hospital												
Female physician colleague												
Present	0.412				0.194				0.649			
Absent												
Medical oncologist colleague												
Present	0.022	1.206	1.032	1.408	0.043	1.261	0.996	1.596	1.000			
Absent		1.000				1.000						
Breast cancer specialized nurse												
Present	0.434				1.000				0.588			
Absent												
Board-certified cancer pharmacist												
Present	0.694				0.136				0.745			
Absent												
Number of breast surgeries per week												
1–5	0.125				0.262				0.903			
6–												
Number of young patients per week												
0–1	0.746				0.273				0.810			
2–												
Partner/spouse												
Present	0.299				0.192				1.000			
Absent												
Children												
Present	0.183				1.000				0.025	1.116	1.029	1.211
Absent										1.000		

Table 3 continued

	I ask co-medical staff if a patient has an interest in fertility				I provide my patients with educational material about fertility preservation				I use LHRH analogue to preserve fertility			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.242				0.125				0.653			
Not fair												
Attitude												
Conservative	0.895				0.100				0.248			
Aggressive												
Gender												
Female	0.133				0.047	1.183	0.973	1.440	0.399			
Male												
Age												
<50	0.262				0.416				0.914			
>50												
Specialty												
Surgery	0.105				0.066				0.057			
Others												
Affiliation												
University hospital/cancer center	0.795				0.046	1.000			0.656			
General hospital/private hospital						1.671	0.959	2.911				
Female physician colleague												
Present	0.793				0.026	1.919	1.014	3.632	0.259			
Absent						1.000						
Medical oncologist colleague												
Present	0.443				0.407				0.381			
Absent												
Breast cancer-specialized nurse												
Present	0.316				0.871				0.516			
Absent												
Board-certified cancer pharmacist												
Present	0.900				0.325				0.663			
Absent												
Number of breast surgeries per week												
1–5	1.000				0.273				0.402			
6–												
Number of young patients per week												
0–1	0.583				0.721				1.000			
2–												
Partner/spouse												
Present	0.192				1.000				0.828			
Absent												
Children												
Present	0.614				1.000				0.156			
Absent												

Table 3 continued

	I consult a reproductive specialist with questions about fertility issues in my patients				I refer patients who have questions about fertility to reproductive specialists			
	p	OR	95% CI		*p*	OR	95% CI	
			Min	Max			Min	Max
Knowledge								
Fair	0.442				0.162			
Not fair								
Attitude								
Conservative	0.032	1.000			0.003	1.656	1.183	2.319
Aggressive		1.599	1.014	2.798		1.000		
Gender								
Female	0.039	1.121	0.995	1.277	0.001	1.176	1.062	1.302
Male		1.000				1.000		
Age								
<50	0.264				0.004	1.424	1.110	1.828
>50						1.000		
Specialty								
Surgery	1.000				0.795			
Others								
Affiliation								
University hospital/cancer center	0.007	1.349	1.067	1.706	0.012	1.243	1.047	1.474
General hospital/private hospital						1.000		
Female physician colleague								
Present	0.051	1.467	0.995	2.164	0.123			
Absent		1.000						
Medical oncologist colleague								
Present	0.103				0.042	1.212	1.011	1.453
Absent						1.000		
Breast cancer-specialized nurse								
Present	0.710				1.000			
Absent								
Board-certified cancer pharmacist								
Present	0.803				0.138			
Absent								
Number of breast surgeries per week								
1–5	0.785				1.000			
6–								
Number of young patients per week								
0–1	0.270				0.813			
2–								
Partner/spouse								
Present	0.807				0.670			
Absent								
Children								
Present	0.197				0.209			
Absent								

of reproductive specialists or infertility clinic for referral (38%) were the major causes for them not to discuss fertility with patients.

Discussion

This study describes the attitude of the main providers of breast cancer treatment in Japan towards fertility issues in young breast cancer patients. The high response rate to our survey in a relatively short time indicates the interest of breast oncologists in fertility issues. More than 80% of the participants responded that they had a positive attitude when discussing fertility issues in the clinic, but this result may be biased by the respondents' interest in fertility issues. The recent awareness of fertility issues among Japanese breast oncologists may be related to the publication of the ASCO guideline in 2006 and the inclusion of fertility-related contents in JBCS patient guideline 2009 [2, 9]. Indeed, the JBCS treatment guideline, the standard textbook for board certification of Breast Oncologists, updated its contents to cover fertility-related issues in July 2010 [10].

The physicians with a positive attitude and working in institutions with medical oncologists and/or female colleagues had a higher likelihood of consultation or referral to reproductive specialists. The likelihood of referring to reproductive specialists was slightly higher in female physicians, which was consistent with the results of the survey in the USA [4]. These results indicate that participation of female healthcare providers in the team and a multidisciplinary working environment might enhance physicians' awareness of and behavior toward fertility-related issues. Because knowledge and attitude seem to be influenced by gender, personal experience, and the working environment of the physicians, we think that outreach with educational materials and systematic learning opportunities for healthcare providers would be helpful in expanding knowledge and performance regarding fertility issues in young breast cancer patients.

High risk of disease recurrence was considered the greatest barrier for physicians, similar to the results of other studies [5, 6]. In our previous study, patients' with higher risk of disease recurrence did not voluntarily express their concerns regarding fertility when compared to patients of lower risk of disease recurrence [3]. Both patients and physicians may refrain from discussing future fertility when the estimation of prognosis of the cancer is poor. Although early referral to reproductive specialists might increase the patients' likelihood of receiving reproductive intervention and improve the fertility outcome [11, 12], fertility preservation techniques such as embryo preservation and oocyte preservation connote ethical issues especially in patients with poor prognosis [13]. Ethical and psychosocial support is necessary in the shared decision-making process among patients, families, and physicians.

A lack of reproductive specialists or infertility clinic for referral is a real problem. A survey in the USA showed that many breast cancer clinicians reported that they do not have knowledge of or resources for fertility preservation [8, 14]. Interdisciplinary communication between reproductive specialists and oncologists is necessary.

Early case–control studies suggest that pregnancy after primary treatment of breast cancer does not have a negative impact on cancer prognosis, although "healthy mother" bias might exist [15]. Because prognostication of breast cancer has become individualized using genetic biomarkers [16, 17], further investigations to clarify the impact of pregnancy after primary treatment on an individual basis is needed so that patients can personalize their decision-making regarding both cancer treatment and fertility.

In conclusion, Japanese breast oncologists were in general positive in discussing fertility issues with young breast cancer patients. Female and younger physicans as well as physicians working in a multidisciplinary environment had more positive attitudes and behavior towards fertility preservation. The development of multidisciplinary and interdisciplinary programs is necessary to meet the fertility needs of breast cancer patients.

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Quantitative assessment of appearance changes and related distress in cancer patients

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Abstract

***Objectives*: This study examined both the frequency of appearance-related symptoms and distress resulting from these symptoms in cancer patients receiving chemotherapy.**

***Methods*: Self-report questionnaires were distributed to 753 outpatients receiving ≧4 weeks of treatment at an outpatient chemotherapy center. Valid responses were returned by 638 patients (response rate, 84.7%). Participants were questioned about 57 appearance-related symptoms (AS) and 23 non-appearance-related physical symptoms (non-AS); psychological well-being was assessed using a shortened version of the Derriford Appearance Scale 59.**

***Results*: Questionnaire responses were obtained from 264 male and 374 female patients (mean age, 59.5 years; range, 18–85 years). Most respondents (80.3%) were concerned with changes in appearance resulting from treatment. By sex and disease type, women suffered more than men, and treatment for breast cancer created the greatest distress for women.**

***Conclusion*: Cancer patients are concerned about a variety of AS, and these may result in greater distress than non-AS. AS-related information and care are increasingly being sought in advance of treatment.**

Introduction

Patient distress is an important factor that impacts greatly on quality of life, psychological well-being (PWB), and treatment decisions and outcomes [1–4]. Advances in medical technology – such as the development of antiemetic drugs and other new medications [5,6] – have led to reductions in distress from the physical symptoms that accompany cancer treatment. However, increases in distress from symptoms of psychosocial origin were pointed out as early as the 1990s [7,8]. This may be attributable to the greater number of patients who now undergo shorter periods of hospitalization [9] and/or continue to lead active lives even while undergoing treatment, thanks to advances in outpatient care therapies and facilities. Patients are thus now more likely to be aware of treatment-related changes in appearance and suffer distress as a result [10–12]. Accordingly, changes in appearance can be considered an important element of distress.

However, with the exception of studies examining such localized treatment-related side effects as scalp alopecia and mastectomy [13–18], little detailed quantitative research has focused on treatment-related changes in appearance as a whole [17,19], and few studies have investigated the impact of cancer type, age, and sex on these appearance problems [10,20].

Accordingly, the present study aimed to elucidate the incidence of appearance changes and the degree of distress due to such changes associated with cancer treatments.

Patients were stratified on the basis of disease and sex and compared in terms of distress experienced because of appearance-related (AS) and non-appearance-related physical symptoms (non-AS). We were thus able to more clearly elucidate the characteristics of distress due to AS.

We investigated dependent variables on the basis of the following two hypotheses. First, with regard to sex, the body awareness of men is considered more likely to focus on functional capabilities, whereas that of women is more likely to focus on appearance [21–23]. The degree of appearance-related distress could thus be expected to differ according to sex, with women experiencing greater distress than men (Hypothesis 1). Second, with regard to age, younger patients may be more likely to focus on appearance than older patients [24]. Younger patients could thus be expected to experience greater levels of distress due to AS (Hypothesis 2).

Methods

Participants

All study participants received chemotherapy on an outpatient basis at the National Cancer Center Hospital (NCCH) in Tokyo between July and October 2009. At the time of distribution of the self-report questionnaire, all participants satisfied the following inclusion criteria: (1) performance status 0–2; (2) age ≧ 18 years; and (3) completion of ≧4 weeks of chemotherapy as calculated from the time of the initial treatment session.

Procedures

During the study period, a list of potential participants was created by continuous sampling of eligible patients

undergoing anticancer therapy at the Outpatient Treatment Center of NCCH. From that list, self-report questionnaires were distributed to 753 patients who signed an informed consent form. Of these, 638 patients returned valid responses by mail (response rate, 84.7%). For each participant, the site of cancer and the chemotherapeutic agents used for treatment were confirmed through the use of electronic medical charts. The study protocol was approved by the institutional review board of the NCCH. Study participants included 202 gastrointestinal cancer patients, 175 breast cancer patients, 69 hepatobiliary/pancreatic cancer patients, 60 hematological cancer patients, 55 lung cancer patients, and 77 patients with other types of cancer.

Measures

The questionnaire was designed to elicit information on the demographic and medical variables of participants, along with the frequency and degree of distress due to non-AS, such as nausea and constipation, and AS, such as hair loss, the presence or absence of concern regarding changes in appearance, and the impact of appearance issues on PWB.

Non-appearance-related symptoms

Griffin *et al.* [7] used 45 comprehensive items in a study evaluating the distress associated with chemotherapy-induced symptoms. For the present questionnaire, we initially selected those 29 items experienced by ≧20% of the participants in the study by Griffin *et al.* After eliminating six AS, we arrived at a total of 23 non-AS items.

(1) With regard to the presence/absence of symptoms, each patient was asked which symptoms they (a) had experienced in the past; (b) were currently experiencing; and (c) had never experienced. If a respondent had experienced a symptom in the past and was also experiencing the same symptom in the present, both responses were checked. (2) Patients were asked to rate the degree of distress using a 4-point scale: 1 (*none*); 2 (*mild*); 3 (*moderate*); and 4 (*severe*). As feelings of wellness are constantly changing, participants were asked to base the assessment of an item on the level of distress perceived at the time of most intense distress. The Japanese translation of the non-AS items from the study by Griffin *et al.* that appeared in our questionnaire, as well as a check of the accuracy of that translation, was prepared after much deliberation by two oncologists and a dermatologist.

In addition, with regard to the total degree of distress due to non-AS, the total points for the items currently being experienced were used as an index (total score calculated using 0 as the score for the degree of distress due to side effects not experienced). This score showed a high internal consistency in this sample ($\alpha = 0.89$).

Appearance-related symptoms

As for the AS items included in our questionnaire, because no previous studies, including that by Griffin *et al.*, have attempted to examine such a wide range of AS in a systematic, comprehensive manner, we decided to supplement eight AS items chosen from the study by Griffin *et al.* with other items derived from interviews with medical staff. Ultimately, 57 items were selected, including 40 chemotherapy-induced items, 14 items resulting from surgical treatment, and three radiation therapy-induced items. The items were then checked and reviewed by two oncologists, along with five oncology nurses from NCCH. In addition, to confirm the validity of the previously mentioned items, a pilot study [25] was conducted on 102 cancer patients with the same cancer tumor-type distribution as the main study participants.

In the pilot study, all 57 items were experienced by at least one patient, whereas there were no entries indicating other symptoms in a 'Comments' column that had been added on an exploratory basis. We thus surmised that the selected items were sufficiently comprehensive.

Using the same method as for non-AS, we inquired the (1) presence or absence of experience of each symptom and (2) degree of distress for each item, and also calculated the total for the degree of distress due to AS. In this sample, as well, this score showed a high internal consistency ($\alpha = 0.92$).

Table 1. Demographic of respondents of the study population ($n = 638$)

	n	%
Age, years		
59.5 ± 11.7 years (mean)		
Gender		
Female	264	58.6
Male	374	41.4
Employment status		
Employed	251	39.4
Unemployed, retired	387	60.6
Marital status		
Married or de facto	492	77.1
Single	49	7.7
Divorced, widowed, or separated	82	12.9
Unknown	15	2.4
Type of cancer		
Gastrointestinal	202	31.7
Breast	175	27.4
Hepatobiliary	69	10.8
Hematological	60	9.4
Lung	55	8.6
Other	77	12.1
Extent of disease		
Local	363	56.9
Metastatic	275	43.1
Months from first chemotherapy		
6.7 ± 8.5 months (mean), range: 0.9–65.4 months		
Other treatments		
Surgical therapy	378	59.4
Radiation therapy	72	11.3
Hormone therapy	17	2.7
Medication		
Taxane	140	21.9
Anthracycline	98	15.4
Platinum	141	22.1
Antimetabolite	276	43.3
Alkylating	93	14.6
Molecular target	202	31.7
Other	134	21.0
Days of external activities per week		
Less than 1 day	246	38.6
3 days	180	28.2
5 days	95	14.9
Every day	117	18.3
Prevalence of concern about appearance changes by gender		
Female	324	86.6
Male	188	71.2

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Table 2. Non-appearance-related symptom frequency and distress by gender and cancer type

	Gastrointestinal cancer			Breast cancer		Hepatobiliary/pancreatic cancer			Hematological cancer			Lung cancer		
	Patients reporting symptom	Mean degree of distress		Patients reporting symptom	Mean degree of distress	Patients reporting symptom	Mean degree of distress		Patients reporting symptom	Mean degree of distress		Patients reporting symptom	Mean degree of distress	
	%	Male (134)	Female (68)	%	Female (174)	%	Male (36)	Female (33)	%	Male (28)	Female (32)	%	Male (29)	Female (26)
Nausea and emesis	68.3	2.48	2.83	74.3	3.14	66.7	2.33	2.28	63.3	3.06	3.35	72.7	2.75	2.80
Fatigue	80.2	2.14	2.64	90.3	2.71	76.8	2.19	2.32	88.3	2.74	3.12	80.0	2.35	2.73
Dizziness	49.5	1.77	2.24	52.0	2.10	50.7	2.00	2.00	56.7	2.25	2.83	58.2	1.88	2.29
Shortness of breath	49.0	1.95	2.55	60.6	2.24	44.9	1.80	2.07	63.3	2.12	2.90	72.7	2.42	2.32
Tinnitus	24.3	1.68	2.05	30.9	1.88	20.3	1.64	2.00	30.0	1.67	2.25	36.4	2.00	1.69
Hot flashes	27.7	1.67	2.17	54.9	2.30	24.6	1.73	1.62	41.7	2.20	2.31	25.5	1.71	2.33
Dry mouth	44.6	1.51	1.91	52.6	1.90	42.0	1.53	1.71	50.0	2.20	2.62	40.0	1.62	2.00
Oral mucositis	64.4	2.33	2.79	71.4	2.70	34.8	1.92	1.92	65.0	2.95	2.63	45.5	2.54	2.45
Taste disturbance	70.8	2.26	2.63	74.9	2.61	55.1	2.05	2.27	68.3	2.37	3.14	70.9	2.32	2.79
Dysosmia	32.7	1.79	2.52	40.6	2.46	43.5	2.00	2.07	38.3	2.27	3.18	43.6	2.50	2.67
Weight changes	70.8	1.64	2.29	63.4	1.83	75.4	1.45	2.00	70.0	2.19	2.09	67.3	1.78	1.59
Appetite changes	76.2	2.27	2.47	69.1	2.21	66.7	2.08	2.35	71.7	2.28	2.70	67.3	2.25	2.27
Constipation	67.8	2.30	2.81	74.3	2.75	63.8	2.63	2.14	73.3	2.44	2.78	70.9	2.20	3.06
Diarrhea	68.3	2.34	2.85	54.3	2.40	55.1	2.29	2.72	45.0	2.27	2.19	50.9	2.33	2.00
Frequent urination	44.6	1.95	2.17	53.7	1.82	43.5	1.67	2.24	55.0	1.80	2.11	47.3	1.77	1.80
Irregular menstruation	10.9	—	1.57	42.0	1.67	13.0	—	1.67	23.3	—	2.50	23.6	—	1.25
Insomnia	50.5	2.00	2.73	62.9	2.28	44.9	2.14	2.28	61.7	2.56	2.53	60.0	2.35	2.46
Pruritus	44.6	2.09	2.48	49.7	2.37	46.4	2.42	2.32	41.7	2.08	2.55	58.2	1.93	2.50
General pain	13.9	2.50	3.10	42.9	2.82	18.8	2.00	2.38	31.7	2.50	3.11	40.0	2.80	3.10
Headaches	28.2	2.04	2.22	51.4	2.55	36.2	2.23	2.30	41.7	2.70	3.08	25.5	2.40	2.57
Treatment site pain	29.7	2.29	2.50	64.0	2.41	44.9	2.15	2.00	40.0	2.44	2.85	29.1	2.14	2.00
Sensory neuropathy	71.3	2.32	2.88	65.1	2.84	37.7	2.25	2.67	76.7	2.55	3.12	65.5	2.50	2.92
Fever	28.7	2.17	2.87	53.1	2.70	36.2	2.25	2.20	50.0	2.79	2.46	30.9	2.44	2.62

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Table 3. Appearance-related symptom frequency and distress by gender and cancer type

	Gastrointestinal cancer			Breast cancer		Hepatobiliary cancer			Hematological cancer			Lung cancer		
	Patients reporting symptom	Mean degree of distress		Patients reporting symptom	Mean degree of distress	Patients reporting symptom	Mean degree of distress		Patients reporting symptom	Mean degree of distress		Patients reporting symptom	Mean degree of distress	
Symptom	%	Male (134)	Female (68)	%	Female (174)	%	Male (36)	Female (33)	%	Male (28)	Female (32)	%	Male (29)	Female (26)
Chemotherapy induced														
Scalp hair loss	73.8	2.12	2.78	96.0	3.47	39.1	1.80	2.26	95.0	2.23	3.44	90.9	2.17	3.17
Loss of eyebrows	39.1	1.85	2.30	80.6	2.77	8.7	1.00	2.14	43.3	1.38	3.00	67.3	2.06	2.61
Loss of eyelashes	29.7	1.74	2.65	74.9	2.76	2.9	1.00	2.33	35.0	1.88	2.73	58.2	2.00	2.58
Loss of vibrissae	21.8	1.59	1.87	64.0	2.16	4.3	1.00	1.50	31.7	1.00	2.12	45.5	1.79	1.82
Lip desquamation	16.3	2.09	2.28	26.9	2.12	13.0	2.00	1.50	30.0	1.80	2.18	18.2	1.00	1.89
Facial discoloration	33.2	1.81	2.82	35.4	2.56	26.1	1.75	2.56	28.3	1.60	2.69	21.8	1.00	2.50
Skin blemishes, under-eye circles	39.1	1.73	2.64	51.4	2.57	27.5	2.00	2.45	36.7	1.67	2.50	23.6	1.80	2.17
Facial dry skin	18.3	2.00	2.44	41.1	2.22	11.6	1.00	2.33	25.0	1.71	2.38	23.6	1.50	2.17
Facial edema	30.7	2.18	2.67	53.7	2.58	26.1	2.43	2.00	36.7	2.62	2.58	36.4	1.71	2.30
Hoarseness	19.3	1.74	2.50	10.3	2.38	2.9	—	2.00	20.0	2.25	3.00	20.0	2.62	—
CV-port	56.4	1.49	2.28	15.4	1.87	8.7	1.25	2.00	6.7	2.33	4.00	3.6	1.00	—
Weight gain	28.7	1.64	1.88	44.0	2.18	18.8	3.00	2.12	13.3	2.33	3.00	27.3	1.71	2.60
Weight loss	56.9	1.63	2.00	44.0	1.42	59.4	1.48	2.28	49.2	1.78	1.95	60.0	1.71	1.54
Fingernail discoloration	49.5	1.69	2.15	80.0	2.39	14.5	1.00	1.50	46.7	1.62	2.47	45.5	1.50	2.29
Transverse furrows on fingernails	38.6	1.57	2.10	68.0	2.29	14.5	1.33	1.50	35.0	1.33	2.38	45.5	1.55	2.23
Split fingernails	37.6	1.95	2.62	46.3	2.75	21.7	1.75	1.67	18.3	1.83	2.00	29.1	2.00	2.75
Fingernail onycholysis	9.9	2.00	2.17	33.1	2.75	4.3	1.00	1.00	10.0	2.00	2.00	18.2	1.67	2.57
Fingernail detachment	12.9	2.07	2.55	31.4	2.61	2.9	2.00	2.00	8.3	1.75	3.00	18.2	2.00	2.40
Hair loss on hands	18.8	1.28	1.57	42.3	1.17	4.3	1.00	2.00	23.3	1.00	1.13	29.1	1.55	1.00
Hand discoloration	38.6	1.67	2.48	29.1	2.48	26.1	1.57	2.00	21.7	1.67	2.90	16.4	1.50	2.25
Dry skin of hands	22.8	1.96	2.05	35.4	1.95	15.9	1.50	2.00	18.3	1.71	2.67	16.4	1.67	2.50
Desquamation of hands	24.3	2.08	2.50	20.0	2.33	8.7	1.00	2.50	13.3	1.33	2.80	16.4	1.60	2.25
Hand edema (lymphedema)	14.9	1.69	2.53	37.1	2.49	10.1	2.25	2.33	20.0	2.29	2.60	21.8	1.67	2.38
Upper limb hair loss	22.8	1.19	1.30	52.0	1.09	1.4	1.00	1.00	26.7	1.00	1.00	34.5	1.42	1.00
Discoloration of upper limbs	10.4	1.44	2.27	14.3	1.91	8.7	2.00	1.80	15.0	1.67	3.33	7.3	2.00	2.50
Dry skin of upper limbs	13.9	1.50	2.00	21.7	1.77	5.8	3.00	2.00	16.7	1.75	2.33	7.3	1.50	2.50
Injection site scar on arms	27.7	1.38	2.05	58.9	2.19	36.2	2.09	2.38	35.0	2.20	2.79	32.7	1.67	2.25
Upper limb edema	3.0	1.33	3.50	35.4	2.53	2.9	—	1.50	6.7	3.00	3.00	9.1	1.00	2.50
Toenail discoloration	43.1	1.50	2.13	71.4	2.06	10.1	3.00	1.57	33.3	1.67	2.36	43.6	1.25	1.86
Transverse furrows on toenails	25.2	1.62	2.05	49.1	2.14	10.1	2.00	1.50	25.0	1.22	2.50	36.4	1.33	2.22
Split toenails	20.8	1.93	2.36	31.4	2.37	8.7	2.50	1.25	11.7	1.50	3.00	16.4	1.75	2.25
Toenail onycholysis	5.4	1.67	1.75	23.4	2.42	2.9	—	1.00	1.7	2.00	—	7.3	—	2.67
Toenail detachment	9.9	2.18	2.50	29.1	2.71	2.9	2.00	1.00	3.3	2.00	—	7.3	1.67	3.00
Lower limb hair loss	26.7	1.18	1.18	57.7	1.09	4.3	1.50	—	35.0	1.08	1.13	45.5	1.40	1.13
Foot discoloration	15.8	1.94	2.47	19.4	2.03	4.3	—	3.00	20.0	3.00	3.00	5.5	1.00	2.00

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Foot desquamation	20.8	2.00	1.84	18.3	2.00	8.7	2.00	2.25	10.0	1.50	2.00	10.9	1.60	2.00
Pedal edema	27.2	2.12	2.82	42.9	2.64	26.1	2.75	2.20	26.7	2.57	2.57	30.9	2.00	2.22
Vulnerable skin	24.3	2.04	2.08	30.3	2.27	17.4	1.50	1.83	28.3	2.57	2.44	14.5	1.67	2.00
Eczema	32.2	2.22	2.47	38.9	2.51	27.5	2.22	2.29	38.3	2.50	2.75	32.7	2.12	2.33
Surgical therapy induced														
Scars on the body surface	58.9	1.48	2.02	68.0	2.76	49.3	1.70	2.67	15.0	1.50	2.80	18.2	1.60	2.00
Mastectomy	0.5	—	1.17	64.6	3.22	4.3	—	2.60	3.3	—	4.00	5.5	—	1.50
Tubes outside of the body, indwelling tubes	14.4	2.07	2.62	25.1	2.22	26.1	2.29	1.90	10.0	3.50	2.75	9.1	3.00	3.00
Stoma	14.9	2.60	3.00	0.6	1.00	2.9	—	3.50	1.7	—	1.00	1.8	2.00	—
Radiation therapy induced														
Radiation dermatitis and ulcers	3.5	1.60	—	28.0	2.24	0.0	—	—	3.3	3.00	1.00	5.5	2.00	3.00

Other (frequency rate < 15%).
Surgical therapy induced: 10 items.
Radiation therapy induced: two items.
Additional cited symptoms: seven items.

Appearance changes and psychological well-being

Unlike physical symptoms such as nausea, appearance changes such as scalp alopecia can not only cause physical distress but also exert a considerable negative impact on mental health as a result of decreased self-esteem and the fear of being deemed unattractive by others. We used a 12-item Japanese version [26] of the Derriford Appearance Scale 59 (DAS-59) [27–29] to measure psychological distress and behavioral impairment in patients concerned with problems of appearance in both clinical and non-clinical populations. This 12-item DAS-derived scale comprised three items selected from each of four DAS-59 factors. With a maximum score of 56 and a minimum score of 0, higher scores on this scale indicated lower levels of PWB in patients with appearance-related concerns.

The 12 items showed a high degree of one-dimensionality in this sample ($\alpha = 0.92$). It was thus concluded that this approach offers a reliable and valid tool.

Statistical analysis

The sociodemographic variables of the study population, cancer types, and the treatment received for the said cancers were specified (Table 1). The frequency and mean degree of distress were tabulated for each AS and non-AS item by both cancer type and sex.

Tables 2 and 3 compile the data for symptom frequencies (percentage of patients reporting symptoms) and mean degree of distress for non-AS and AS. Table 4 lists the 20 most distressful symptoms by sex for gastrointestinal and breast cancer patients. For AS, the difference in total distress scores between men and women was tested using the *t*-test, whereas differences between diseases were tested by one-way analysis of variance. Correlation analysis was also performed to elucidate relationships to variables such as age (Table 5).

Results

Survey response

A significant number of female participants in the 638-participant study population reported being 'concerned about some aspect of appearance' ($\chi^2(1) = 23.22, p < 0.01$) (Table 1). A *t*-test analysis demonstrated no difference between mean ages of female and male participants by cancer type.

Frequency and degree of distress from non-appearance-related symptoms

There were also many non-AS, which were experienced by more than 60% of patients. Of the non-AS reported, the most frequently cited (76.8–90.3%) was 'fatigue' (Table 2).

Analysis of differences between the sexes in total degree of distress scores for non-AS associated with each disease revealed no significant differences other than for gastrointestinal cancer (men, 21.11 ± 12.69; women, 28.75 ± 15.04; $t(200) = 3.79$; $p < 0.00$).

Frequency and degree of distress from appearance-related symptoms

Table 3 shows the frequency and mean degree of distress for each AS by both sex and cancer type. Items with a

Table 4. Twenty most distressful symptoms of chemotherapy by gender

	Gastrointestinal		Breast
	Male ($n=134$)	Female ($n=68$)	Female ($n=174$)
Rank	Symptom	Symptom	Symptom
1	Stoma[a]	Stoma[a]	Scalp hair loss[a]
2	Nausea and emesis	Sensory neuropathy	Removal of a breast[a]
3	Diarrhea	Fever	Nausea and emesis
4	Oral mucositis	Diarrhea	Sensory neuropathy
5	Sensory neuropathy	Nausea and emesis	General pain
6	Constipation	Facial discoloration[a]	Loss of eyebrows[a]
7	Treatment site pain	Pedal edema[a]	Loss of eyelashes[a]
8	Appetite changes	Constipation	Scars on the body surface[a]
9	Taste disturbance	Oral mucositis	Constipation[a]
10	Eczema[a]	Scalp hair loss[a]	Split fingernails[a]
11	Facial edema[a]	Insomnia	Fingernail onycholysis
12	Fever	Facial edema[a]	Fatigue[a]
13	Fatigue	Loss of eyelashes[a]	Toenail detachment
14	Scalp hair loss[a]	Skin blemishes, Under-eye circles[a]	Oral mucositis
15	Pedal edema[a]	Fatigue	Fever
16	Lip desquamation[a]	Taste disturbance	Pedal edema[a]
17	Pruritus	Split fingernails[a]	Taste disturbance[a]
18	Hand discolorations[a]	Shortness of breath	Loss of fingernails
19	Scratch easily[a]	Hand edema (lymphedema)[a]	Facial edema[a]
20	Headaches	Dysosmia	Skin blemishes, under-eye circles[a]

[a]Appearance-related symptom

Table 5. Correlations between degree of appearance-related symptom

	Gastrointestinal		Breast	Hepatobiliary		Hematological		Lung	
	Male	Female	Female	Male	Female	Male	Female	Male	Female
DAS	0.26***	0.32***	0.22***		0.64***		0.33*	0.56***	
Age		−0.39***				−0.33*			−0.34*

*$p > 0.10$,
**$p > 0.05$,
***$p > 0.01$.

≧15% frequency for at least one cancer type are presented in this table. Although the frequency of AS occurrence differed according to cancer type, virtually no part of the body was not associated with some type of AS.

For each disease, the 20 most distressful symptoms occurring at a frequency of ≧15% were compared for sex differences in the degree of distress. Table 4 shows data for gastrointestinal cancers and breast cancer, which accounted for the largest number of patients in the sample. Comparison of the sex differences in total distress score due to appearance changes associated with each disease found that women experienced significantly greater distress than men for each of the analyzed diseases except for hematological cancer: gastrointestinal (men, 17.09 ± 13.58; women, 31.63 ± 19.84; $t(200) = 6.12$; $p < 0.00$), hepatobiliary/pancreatic (men, 9.14 ± 8.57; women, 16.30 ± 14.62; $t(67) = 2.58$; $p = 0.02$) and lung (men, 16.66 ± 13.28; women, 26.46 ± 15.61; $t(53) = 2.52$; $p = 0.02$).

Differences among diseases were also tested for significance. Because breast cancer was limited to women, single-factor analysis of variance was performed using the disease, and sex was handled as an independent variable, whereas total distress score relating to appearance was considered a dependent variable. The results revealed a significant difference as a function of group ($F(8, 551) = 23.87$; $p < 0.00$). Multiple comparisons performed using Tukey's method showed the breast cancer (female) group had experienced a significantly higher degree of stress due to changes in appearance compared with all other groups. Data for each group were as follows: gastrointestinal cancer male (17.09 ± 13.58); gastrointestinal cancer female (31.63 ± 19.84); breast cancer female (41.02 ± 24.79); hepatobiliary/pancreatic cancer male (9.14 ± 8.57); hepatobiliary/pancreatic cancer female (16.30 ± 14.62); hematological cancer male (17.68 ± 17.23); hematological cancer female (26.00 ± 21.92); lung cancer male (16.66 ± 13.28); and lung cancer female (24.46 ± 21.94).

Correlation with degree of distress from appearance-related symptoms

Correlation analysis was performed for the degree of distress due to changes in appearance and age and DAS scores. Table 5 shows that degree of distress correlated negatively with age but positively with DAS score.

Discussion

There were as many as 80% of cancer patients concerned about changes in appearance arising as a result of therapy. In fact, although differences were seen as a function of the type of cancer and the sex of the patient, changes in appearance occurred broadly throughout the body as a

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whole, and in some cases, the distress associated with them was greater than that for non-AS such as fever.

In most patients, total distress score for AS showed a difference by sex in comparison with non-AS. That is, women felt greater distress than men with regard to symptoms that affected their appearance. The results also indicated differences in the causes of distress in patients. As exemplified by the case of gastrointestinal cancer, the highest ranked 20 items for male participants were primarily non-AS. The AS that appeared on the top 20 list were largely symptoms that impacted physical function, such as pedal edema that rendered walking more difficult. Female participants were more aware of appearance [21,22]. Distress related to hair loss, for example, was felt more strongly by female participants. Similarly, although not causing physical pain or itching, visible symptoms such as eyelash loss and facial discoloration were often ranked higher than typical non-AS. No distress was associated with lower limb hair loss. The greater distress experienced by female participants relative to AS may be an extension of a greater awareness and concern seen in women, in general, relative to beauty and cosmetic [30–32]. In the comparison of the diseases, this was especially true for the group of female patients with breast cancer. This finding supports Hypothesis 1.

The greater the distress due to AS, the higher the DAS score, while PWB decreased. With regard to patient age, the study results supported Hypothesis 2, not for all disease types but for women with gastrointestinal cancer, men with hematological cancer, and women with lung cancer.

This study had certain limitations. The sample was limited to patients in a single cancer treatment center in a major urban area. Future research should be undertaken to expand the number and geographical diversity of treatment centers.

In conclusion, as the frequency of symptoms and the degree of distress associated with AS are quite high, hospitals need to start providing information and care related to appearance [33–35].

This study quantitatively elucidated high-priority items, attributes, and diseases, and the results will be able to serve as basic data for the development of support programs focused on symptoms representing the source of great distress to cancer patients.

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ORIGINAL ARTICLE

Safety of adjuvant trastuzumab for HER-2-overexpressing elderly breast cancer patients: a multicenter cohort study

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Abstract
Background For targeting anti-HER-2, trastuzumab-incorporated chemotherapy is the standard for HER-2-overexpressing breast cancer in adjuvant settings. But there are few data on trastuzumab in elderly patients. We evaluated the incidence of adverse events among an elderly population of trastuzumab-treated HER-2-positive breast cancer patients in adjuvant settings.
Methods Data on 39 elderly HER-2 overexpressing breast cancer patients treated with both curative surgery and adjuvant trastuzumab were retrospectively collected from a Japanese multicenter study. The loading dose was 8 mg/kg body weight, and the maintenance dose was 6 mg/kg every 3 weeks; or the loading dose was 4 mg/kg followed by 2 mg/kg weekly as maintenance.
Results After a median follow-up of 20.0 (2.4–53.9) months, a total of 32 patients (82.1%) completed 1-year trastuzumab treatment. The median treatment duration was 12.0 months (range 2–12; mean 10.5). Adverse events occurred in 11 patients (28.2%). Four (10.2%) discontinued or interrupted treatment after experiencing toxicity. One patient died because of interstitial pneumonia. Three patients (7.7%) had congestive heart failure (CHF), one of whom had a history of angina. Three patients (7.7%) had a lower left ventricular ejection fraction (LVEF), and brain natriuretic peptide elevation was totally observed in three patients (7.7%). Three patients with lower LVEF had received chemotherapy containing doxorubicin before trastuzumab. Of the three patients, two discontinued therapy

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because of CHF, but all recovered with proper medication containing a diuretic agent.
Conclusions Elderly patients tolerated trastuzumab well, although careful management is needed.

Keywords Breast cancer · HER-2/*neu* · Trastuzumab · Elderly

Introduction

The human epidermal growth factor receptor 2 (HER-2) protein is a unique and useful target for antibody therapy against breast cancers overexpressing the HER-2/*neu* gene. HER-2 is overexpressed in 15–25% of human breast cancers [1–3] and correlates with poor clinical prognosis in women with both node-positive and node-negative disease [4–6]. Overexpression of HER-2 has also been associated with potentially more aggressive tumors. As an anti-HER-2-targeting treatment, trastuzumab with chemotherapy is a standard adjuvant systemic therapy for HER-2-positive primary breast cancer [7–10]. However, trastuzumab treatment is also associated with cardiac dysfunction and congestive heart failure (CHF) [11–15]. Recently, a long-term assessment in the herceptin adjuvant (HERA) trial found that the incidence of cardiac endpoints remained low [16]. On the other hand, there have been few data on trastuzumab treatment in elderly patients because in these pivotal adjuvant clinical trials all patients had received standard chemotherapy according to the inclusion criteria. Cardiac toxicity associated with anthracycline-containing chemotherapy in older women with breast cancer is well known [17, 18], so caution is necessary for elderly patients. Thus, we sought to evaluate the incidence of adverse events in an elderly population of HER-2-positive breast cancer patients treated with trastuzumab in an adjuvant setting.

Patients and methods

The data on 39 elderly (≥69 years) HER-2 overexpression breast cancer patients who had been treated with both curative surgery and adjuvant trastuzumab from January 2006 to February 2009 were retrospectively collected from a Japanese multicenter study. The patients did not have cardiac symptoms, uncontrolled hypertension, uncontrolled arrhythmia, or coronary artery disease in practical settings.

Adjuvant chemotherapy had been given according to the investigators' preference. Patients diagnosed with hormone-receptor-positive neoplasia were given endocrine therapy. Radiation therapy was performed in patients who had undergone breast-conserving surgery.

HER-2 status was determined by immunohistochemical (IHC) staining or amplification on fluorescence in situ hybridization (FISH). IHC scores of 3+ or FISH positive (ratio of HER-2:CEP17 ≥2) were regarded as positive. The loading administration dose of trastuzumab was 8 mg/kg of body weight, and the maintenance dose was 6 mg/kg every 3 weeks. Alternatively, the loading dose was 4 mg/kg followed by 2 mg/kg weekly as a maintenance dose. Cardiac function was determined by the left ventricular ejection fraction (LVEF) on echocardiography during trastuzumab treatment. The schedule of cardiac monitoring including brain natriuretic peptide (BNP) during the treatment was not defined. CHF was defined by symptoms, physical signs and objective findings; it included an LVEF drop of 10% or a drop to an absolute LVEF of 50% by the obtained echocardiogram. The severity of adverse events (AEs) was evaluated by the use of the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 3.0). Patients were monitored for clinical effects and drug-related AEs.

Results

Patients

Table 1 shows the characteristics of 39 patients. The mean age was 72.3 (69–84). As adjuvant chemotherapy, 27

Table 1 Patient characteristics ($n = 39$)

Mean age, years (range)	72.3 (69–84)
Primary stage	
I	8
II	25
III	6
Histological grade	
1	6
2	3
3	29
unknown	1
Hormone receptor	
ER (+) and/or PgR (+)	12
ER (−) and PgR (−)	27
Adjuvant chemotherapy	
Anthracyclines and taxanes	6
Anthracyclines, no taxanes	19
Taxanes, no anthracyclines	1
CMF	1
No cytotoxic chemotherapy	12
Adjuvant hormone therapy	
Aromatase inhibitor	11
Tamoxifen	1
No	27

patients (69.2%) had sequential chemotherapy. Of those, 25 (92.6%) had an anthracycline-containing regimen. For six of these patients, this consisted of FEC/FAC: fluorouracil 500 mg/m^2, epirubicin 75–100 mg/m^2, doxorubicin 40–60 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks for more than four cycles; or AC: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles and taxane (paclitaxel or docetaxel). In 19 patients, the anthracycline-containing regimens included the following. One patient had CMF (cyclophosphamide 100 mg orally on days 1 to 14, methotrexate 40 mg/m^2 on days 1 and 8 intravenously, and fluorouracil 600 mg/m^2 intravenously on days 1 and 8, every 4 weeks for six cycles); one had TC (docetaxel 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles; and 12 patients (30.8%) had trastuzumab therapy without chemotherapy.

Safety and tolerability

After a median follow-up time of 20.0 (2.4–53.9) months, a total of 32 patients (82.1%) had completed receiving trastuzumab for 1 year. The median duration of treatment was 12.0 months (range, 2 to 12 months; mean, 10.5 months). Two patients (5.1%) are continuing treatment because they have not completed 1 year; three patients (7.7%) discontinued treatment because of toxicity; one patient (2.6%) had interrupted treatment because of toxicity but was reintroduced after recovery; one patient (2.6%) discontinued after relapse. Adverse events are shown in Tables 2 and 3. Adverse events occurred in 11 patients (28.2 %). One patient died after toxicity led to interstitial pneumonia (IP). She had been undergoing hormone therapy (anastrozole) with trastuzumab after irradiation for the breast. In the CT scan the density of pneumonia was detected almost in accordance with the irradiation area. From the autopsy, it was diagnosed as IP that had been induced by neither infection nor carcinomatous lymphangiosis. The cause of IP was not specified and not significantly related to trastuzumab, although it should not always be denied directly. Three patients (7.7%) had CHF, 2 of whom complained of systemic edema, and 3 had dyspnea. One of these three CHF patients had a history of angina. In particular, regarding cardiotoxicity examinations, three patients (7.7%) had lower LVEF, of whom two also had elevated BNP. BNP elevation was totally observed in three patients (7.7%). Three patients with lower LVEF had been receiving chemotherapy containing doxorubicin immediately prior to the initiation of trastuzumab treatment. Two of the three patients with lower LVEF were discontinued because of CHF, but all recovered with proper medication containing a diuretic agent.

We here present a case of CHF in a 70-year-old female diagnosed with left breast cancer: T1c, N1, M0, stage IIA. Her pathology was estrogen-receptor-positive, progesterone-receptor-negative, and HER-2-positive (3+; IHC). She had received FAC neoadjuvant chemotherapy (the doxorubicin cumulative dose was 260 mg/m^2), followed by 12 courses of weekly paclitaxel. The points of EF and BNP before chemotherapy were 64% and 12.1 pg/ml, respectively. The cardiothoracic ratio (CTR) was 51.3% (Fig. 1a). After she completed chemotherapy, she underwent surgery, after which she received tamoxifen and irradiation for the chest wall, supraclaviculares, and parasternal lymph nodes. After completion of irradiation, trastuzumab treatment was begun. At this time, the point of EF was 73%. The loading administration dose of trastuzumab was 8 mg/kg body weight, and the maintenance dose was 6 mg/kg every 3 weeks. After three cycles of trastuzumab, she experienced dyspnea and leg edema. The point of EF was decreased from 73 to 53%, BNP was

Table 2 Adverse events ($n = 39$)

Events	Grade (G); patients (%)
Acute infusion reaction	G1; 6 (15.4)
Edema	G1; 1, G2; 1 (5.1)
Dyspnea	G1; 1, G3; 2 (7.7)
Rash	G1; 1, G2; 1 (5.1)
Nail change	G1; 2 (5.1)
Interstitial pneumonia	G5; 1 (2.6)
Left ventricular systolic dysfunction	G1; 1, G3; 2 (7.7)
Elevated brain natriuretic peptide	3 (7.7)

Table 3 Adverse events (grade 2–5)

Age	Chemotherapy	Trastuzumab treatment	Cardio-toxicity	Ejection fraction (%)	Pulmonary-toxicity	Duration of trastuzumab (months)
76	None	Tri-weekly	None	62–67	Interstitial pneumonia	2
77	None	Tri-weekly	CHF[a]; G3	69–68	None	5
71	CAF (ADM 300 mg/m^2)	Tri-weekly	CHF[a]; G3	70–49	None	8
70	CAF (ADM 260 mg/m^2), weekly PTX	Tri-weekly	CHF[a]; G2	73–53	None	2

[a] Congestive heart failure

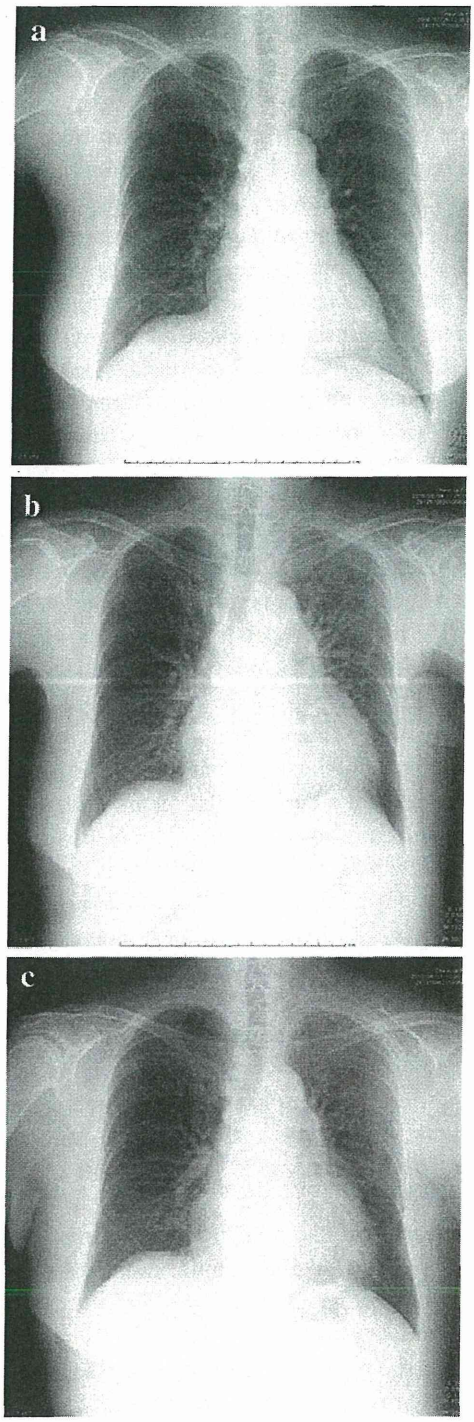

Fig. 1 **a** The points of EF and BNP before chemotherapy were 64% and 12.1 pg/ml, respectively. The cardiothoracic ratio (CTR) was 51.3%. **b** After three cycles of trastuzumab, our patient had dyspnea and leg edema. The point of EF was decreased from 73 to 53%, BNP was elevated from 12.1 to 40.7 pg/ml, and CTR was 60.5%. **c** After 1 week, her heart function had recovered, the point of CTR had decreased from 60.5 to 54.8%, and BNP had also decreased from 40.7 to 9.3 pg/ml

elevated from 12.1 to 40.7 pg/ml, and the CTR was 60.5% (Fig. 1b). She was diagnosed with heart failure (grade 2) by a cardiologist and given a diuretic agent, furosemide (80 mg/day). After 1 week, her heart function had recovered, the point of CTR had decreased from 60.5 to 54.8%, and the BNP had also decreased from 40.7 to 9.3 pg/ml (Fig. 1c). Trastuzumab was reintroduced after LVEF recovery without any other problems.

Outcomes

Of the 39 patients, 2 (5.1%) died; 1 of these deaths was caused by IP, while the other was non-breast cancer-specific deaths. Thirty-six patients (92.3%) were free of relapse, and one had distant metastasis. All patients who completed 1 year of treatment have experienced no more cardiotoxicity or other adverse events.

Discussion

Treatment of breast cancer with trastuzumab is complicated by cardiotoxicity [19]. Cardiac safety in major adjuvant trials is shown in Table 4. The incidence of cardiac endpoints after a long-term assessment in the HERA trial was recently reported. The incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%), that of severe CHF was 0.8%, and that of confirmed significant LVEF decreases was 3.6% [16]. In the other pivotal studies [10, 20, 21], the cardiac event rate was highest in the anthracycline-containing trastuzumab patients (1.9–3.8%) and lowest in patients who had received the regimen of docetaxel, carboplatin, and trastuzumab (TCH) (0.4%). But there are not enough data available on trastuzumab treatment in elderly patients. Thus, it was necessary to evaluate the incidence of adverse events, in particular cardiotoxicity, in an elderly population of HER-2-positive breast cancer patients.

Although the patient population in this study was small, we presented safety data on trastuzumab for elderly breast cancer patients. Overall, the incidence of adverse events was low. Only four patients (10.2%) discontinued treatment because of toxicity. Three patients (7.7%) had CHF, but all recovered with proper medication containing a diuretic agent. As for the treatment for heart failure (HF) caused by trastuzumab-induced cardiotoxicity, in most patients it is reversible [19, 22–25]. LVEF improves after trastuzumab withdrawal and with, or sometimes without, the initiation of HF therapy [19]. Although the identification of patients at risk for trastuzumab-induced cardiotoxicity and the prediction of LVEF recovery have never been investigated, recently troponin 1 was found to be a predictive risk factor for cardiotoxicity, and patients with troponin 1 elevation were unlikely to recover from cardiac dysfunction despite HF therapy [19].

Table 4 Cardiac safety in the four major adjuvant trials

Trial	ARM	Baseline LVEF (%)	CHF[a] (%)	Cardiac death (*n*)
HERA [16]	H 1 year	≥55	0.6	0
	Nil		0	1
NSABP B-31 [21]	AC → P	≥50	0.9	1
	AC → PH		3.8	0
N9831 [20]	AC → P	≥50	0.2	1
	AC → PH		2.5	1
BCIRG 006 [10]	AC → D	≥50	0.4	0
	AC → DH		1.9	0
	D Carbo H		0.4	0

[a] Congestive heart failure

Trastuzumab is indicated for HER-2-positive patients according to the ASCO/CAP guideline [26]. Especially for elderly patients, there is clinical significance to demonstrating the benefit of trastuzumab without toxicity induced by chemotherapy. We have thus been investigating clinical positioning between trastuzumab monotherapy and a combination of trastuzumab and chemotherapy based on a randomized controlled trial in women aged over 70 years with HER-2-positive primary breast cancer [27]. Our hypothesis is that the trastuzumab monotherapy group is not inferior to the trastuzumab and chemotherapy group in disease-free survival, and is superior in safety and health-related quality of life; these are registered as protocol ID: UMIN000002349 for the University Hospital Medical Information Network (UMIN) and protocol ID: NCT01104935 for ClinicalTrials.gov. To prepare this multicenter study, we collected trastuzumab treatment data to ascertain the feasibility of this treatment for elderly patients.

In summary, elderly patients tolerated trastuzumab well, although careful management is needed. Prospective data on a larger number of elderly patients are needed in order to confirm the safety of trastuzumab treatment in elderly patients.

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Conflict of interest The authors state that they have no conflict of interest.

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がん患者コホート研究
——予後改善へのエビデンス
Prospective studies of cancer survivorship：Prognosis and QOL

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◎診断・治療技術の向上や人口構成の変化，生活習慣の変化など，さまざまな要因を背景に，がんサバイバー，すなわちがんを抱えながら生活する人が増えている．患者の立場からは再発の不安も大きく，日常生活のなかでも再発を防ぐために努力をしたいという思いは強いが，再発や死亡といった予後に関連する生活習慣を明らかにするエビデンスレベルの高い疫学研究が，日本のみならず世界的にも不足している．そのため，再発予防のためのがん患者への指針については明確な推奨がなく，「がん患者を含めたすべての人が，がん予防のための推奨事項に従う」との記載にとどまっている．そのような現状を背景に近年，乳がんを中心に，生活習慣と予後との関連を調べる大規模前向き疫学研究が開始され，患者の予後向上と療養生活の質の向上につながることが期待されている．本稿では，国内外の乳がん大規模疫学研究の進展について報告するとともに，著者らが開始した大規模前向き乳がんコホート研究である Rainbow of KIBOU Study について紹介する．

Key word：がん患者，乳がんコホート，再発，予後，生活習慣，ROK Study

がん患者の再発予防のための生活習慣

がんの発症にかかわるリスクファクターについては，本特集でこれまで述べられてきたように，JPHC Study(Japan Public Health Center-based Prospective Study)をはじめとするさまざまな疫学研究の蓄積により，生活習慣とがんの発症に関して多くのエビデンスが構築されている．しかし，がんの再発については，再発や死亡といった予後に関連する生活習慣を明らかにするエビデンスレベルの高い疫学研究が，日本のみならず世界的にも不足している．

そのため生活習慣を中心に，がんの発症や再発との関連を検討した研究のシステマティックレビューを行い作成されたアメリカがん協会(American Cancer Society：ACS)の“Guidelines on Nutrition and Physical Activity for Cancer Prevention”[1]や，世界がん研究基金/アメリカがん研究財団(World Cancer Research Fund：WCRF/American Institute for Cancer Research：AIC)の“Food, nutrition, physical activity and the prevention of cancer：a global perspective”[2]でも，予後(再発，死亡)をエンドポイントとしたエビデンスレベルの高い研究がきわめて少ないため，再発予防のためのがん患者への指針については明確な推奨がなく，「がん患者を含めたすべての人が，がん予防のための推奨事項に従う」との記載にとどまっている．

がん患者を対象とする大規模前向き疫学研究

診断・治療技術の向上や人口構成の変化，生活習慣の変化など，さまざまな要因を背景に，がんサバイバー，すなわちがんを抱えながら生活する人が増えている．効果のある治療法が存在しても，患者の立場からは再発の不安も大きく，日常生活のなかでも再発を防ぐために努力をしたいという思いが強い．とくに食事や運動，病気との付き合い方など，自分でも変更が可能な生活習慣の