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Phase II Trial of Preoperative Chemotherapy for Breast Cancer: Japan Breast Cancer Research Network (JBCRN)-02 Trial

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Abstract. *Background: Neoadjuvant chemotherapy (NAC) is one of the main strategies for patients with locally advanced breast cancer. In our previous study, biological markers such as estrogen receptor (ER), progesterone receptor (PgR), and HER2 were essential predictors of the effectiveness of NAC to help individualize treatment. This study examined the effect of NAC on the disease-free survival (DFS) of breast cancer patients. Furthermore, the study was expanded by adding Ki-67 as a biological marker, and examined the correlation between Ki-67 and the prognosis. Patients and Methods: Between September 2005 and September 2007, 43 patients with breast cancer received NAC and surgery. Four cycles of DC (doxorubicin: 60 mg/m^2, and cyclophosphamide: 500 mg/m^2) were administered intravenously (i.v.) on day 1 every 21 days, followed by 12 cycles of paclitaxel i.v. (80 mg/m^2) every 7 days, prior to surgery. The primary endpoint was the pathological complete response (pCR) rate and the secondary endpoint was DFS; the pCR rate was estimated for each groups stratified by the presence or absence of different factors (PcR, ER/PgR, and Ki-67). Results: The clinical response (cCR+cPR) rate was 81.0%, and the pCR rate was 25.6%. The pCR rate was 75, 50, 9 and 0% in HER2$^+$/ER$^-$, HER2$^+$/ER$^+$, HER2$^-$/ER$^-$, and HER2$^-$/ER$^+$ patients, respectively. The 4-year DFS rate was estimated at 78% for all patients. The HER2 status was an independent predictor of pathological complete response (pCR). The DFS rate of patients with lower Ki-67 values (<15%) was higher than that of patients with higher Ki-67 values (≥15%). The treatment-related adverse events were manageable: the majority were mild, but five patients experienced grade 3 (neutropenia and sensory neuropathy) adverse events. Conclusion: DC followed by weekly paclitaxel is an active and manageable preoperative regimen for breast cancer patients. HER2 overexpression may be a good predictive marker of pCR, and the Ki-67 value after NAC may be a prognostic factor for DFS.*

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Neoadjuvant chemotherapy (NAC) has emerged as a promising step forward in the management of locally advanced breast cancer. When administered before surgery, chemotherapy may induce tumor shrinkage, facilitate surgery, and increase the breast-conserving surgery rate (1-3).

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-27 demonstrated that compared to preoperative DC alone, the addition of sequential docetaxel doubled the pathological complete response (pCR) rate, increased the clinical complete response (cCR) rate, and increased the proportion of patients with negative axillary nodes (3-5). Some studies demonstrated that patients with pCR to chemotherapy had a good prognosis (1-5). Therefore the pathological response is an important prognostic parameter that can be used as a surrogate parameter for clinical outcomes. Furthermore, preoperative systemic therapy administering molecular targeted therapies, such as trastuzumab (Herceptin), and new hormone blockers, such as aromatase inhibitors, have been added to these regimens for the past 10 years (6). However pathological response cannot be accurately predicted.

In our previous study, biological markers such as estrogen receptor (ER), progesterone receptor (PgR), and HER2 were essential predictors of the effectiveness of NAC to help individualize treatment (7). This study examined the effect of NAC on the disease-free survival (DFS) of breast cancer

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Table I. *Response criteria used in the present study.*

Grade 0 (negative)	Almost no changes in post-treatment cancer cells.
Grade 1 (slight)	
1a (mild)	Slight changes observed in cancer cells regardless of lesion size.
	Significant changes observed in <1/3 of cancer cells.
1b (moderate)	Significant changes observed in 1/3 to <2/3 of cancer cells.
Grade 2 (significant)	Significant changes observed in approximately ≥2/3 of cancer cells.
Grade 3 (complete)	All cancer cells necrotize or disappear, replaced with granuloma-like tissues or focal fibrosis.

patients. In addition, we expanded the study by adding Ki-67 as a biological marker. We conducted a multicenter prospective neoadjuvant trial with four cycles of doxorubicin and cyclophosphamide (DC) followed by twelve cycles of paclitaxel for breast cancer patients to investigate the relationship between pathological effect and survival. Clinical response, the rate of breast-conserving surgery (BCS), some factors, and safety were also evaluated.

Patients and Methods

This multicenter, open-label, single-arm, phase II study was conducted in women aged 20 to 69 years with previously untreated unilateral carcinoma of the breast (T2-3, N0-1, M0). Patients with bilateral, locally advanced, or metastatic disease were excluded. Other eligibility criteria included: Eastern Cooperative Oncology Group performance status 0 to 1; adequate bone marrow reserve (absolute neutrophil count (ANC) >2,000/mm^3, platelet count >100,000/mm^3), and adequate renal (serum creatinine <1.5 times upper normal limit) and hepatic function (total bilirubin <2 times upper normal limit); left ventricular ejection fraction (LVEF) within normal limits based on echocardiographic (ECG) assessment. Patients were excluded from the study if they had any history of another neoplasm. All patients gave written informed consent before their participation in the trial. The study was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Review Boards at all participating centers, and written informed consent was obtained from all patients prior to the study.

Four cycles of DC (doxorubicin: 60 mg/m^2 and cyclophosphamide: 500 mg/m^2) administered intravenously (*i.v.*) on day 1 every 21 days were followed by 12 cycles of paclitaxel *i.v.* (80 mg/m^2) every 7 days, prior to surgery. Treatment was continued in the absence of unacceptable toxicity. Premedication 30 min prior to paclitaxel administration consisted of *i.v.* ranitidine (50 mg), and *i.v.* dexamethasone (20 mg), and oral diphenhydramine (50 mg). Prophylactic hematologic growth factor support was prohibited before the second course of treatment.

The disease status was confirmed by physical examination, mammography, and breast ultrasonography and a core or fine-needle biopsy for histopathological diagnosis. During treatment, white blood cell count was repeated weekly. Biochemistry tests were performed after courses 2 and 4, and cardiac monitoring comprised an ECG after course 4 and LVEF measurement after courses 2 and 4, or after study discontinuation. Adverse events were evaluated according to CTC grades.

Treatment was to be postponed for a maximum of 2 weeks for severe toxicity. If toxicity did not improve during this period, chemotherapy was discontinued and surgery was recommended. Dose reductions of doxorubicin from 60 to 40 mg/m^2, cyclophosphamide from 600 to 400 mg/m^2, and paclitaxel from 80 to 60 mg/m^2 were permitted in cases of febrile neutropenia and grade 3 or 4 non-hematological toxicities except for nausea, vomiting, and fatigue. Following chemotherapy and clinical assessment of the response, patients underwent surgery. If the tumor was too large or invasive for BCS, modified radical mastectomy was recommended. Sentinel lymph node biopsy was not performed to confirm the disease stage.

Assessment of response to therapy. A physical examination was performed and the performance status was assessed on day 1 of each course. Tumor assessment involved a physical examination before, during, and after every course and breast ultrasonography after 4 courses of DC regimen; the appearance of any new lesion was documented. The primary endpoint was to determine the rate of pCR induced by primary chemotherapy and assessment of the pathological response as an independent predictor of DFS. The pathological response was classified according to the criteria in Table I.

The clinical response of bidimensionally measurable and assessable disease was classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to WHO criteria. CR was defined as the disappearance of all clinical evidence of the tumor; PR was defined as a 50% or more reduction in the sum of the products of measured lesions, or an estimated decrease in the tumor size of at least 50%, without the appearance of new lesions; SD was defined as a decrease in the lesion size of less than 50% for the sum of the products of measured lesions, or an estimated decrease of less than 50% and increase of less than 25%, without the appearance of new lesions. Any measured or estimated increase greater than 25% or the appearance of new lesions was defined as PD. The clinical response was defined as the sum of CRs and PRs. Surgery was to be performed less than 4 weeks after the last chemotherapy course.

Where possible, breast-conserving methods were carried out, taking into account the residual tumor size after chemotherapy, and esthetics. After a complete clinical response to chemotherapy, when feasible, a wide surgical excision was performed to remove the tumor with free margins without deforming the breast. Postoperative irradiation was delivered to the breast and regional lymph nodes according to local practices. After chemotherapy, a mastectomy was carried out if the initial multifocal disease could not be removed by a single wide excision or if an extensive area of radiological microcalcifications did not regress with chemotherapy (even though a cCR had been achieved). Hormonal treatment with tamoxifen was given to all patients with ER$^+$ tumors, and any additional chemotherapy was administered at the discretion of the investigator. Follow-up was performed every 4 months for the first 2 years, thereafter every 6 months, and once a year after 5 years. A total of 43 assessable patients were enrolled in the study.

Table II. *Patient characteristics, n (%).*

Stage	1	2 (4.7%)
	2a	10 (23.3%)
	2b	17 (39.5%)
	3a	6 (14.0%)
	3b	3 (7.0%)
	3c	5 (11.6%)
Tumor size (mm)	<20	4 (9.3%)
	20 +	39 (90.7%)
ER	Positive	28 (65.1%)
	Negative	15 (34.9%)
PgR	Positive	25 (58.1%)
	Negative	18 (41.9%)
HER2	0	19 (44.2%)
	1+	5 (11.6%)
	2+	5 (11.6%)
	3+	14 (32.6%)
Pathological grade	1	15 (34.9%)
	2	24 (55.8%)
	3	3 (7.0%)
	Unknown	1 (2.3%)
Lymph-node status	0	27 (62.8%)
	1-3	9 (20.9%)
	4+	5 (11.6%)
	Unknown	2 (4.7%)

Table III. *Prediction of pCR (G3) by logistic regression.*

Factors	% pCR	Statistics	Univariate analysis	Multivariate analysis
Age				
<50 years	23.8% (5/21)	OR	1.19	1.80
≥50 years	27.3% (6/22)	*P*-value	1.000	1.000
Tumor size				
<30 mm	0.0% (0/7)	OR	3.92	3.82
≥30 mm	30.6% (11/36)	*P*-value	0.209	0.288
ER				
–	40.0% (6/15)	OR	2.98	1.19
+	17.9% (5/28)	*P*-value	0.225	1.000
PgR				
–	38.9% (7/18)	OR	3.24	0.93
+	16.0% (4/25)	*P*-value	0.180	1.000
HER2				
2+	6.9% (2/29)	OR	21.72	21.07
3+	64.3% (9/14)	*P*-value	<0.001	0.003
Clinical response				
SD+PD	11.1% (1/9)	OR	3.26	3.17
CR+PR	29.4% (10/34)	*P*-value	0.510	0.762

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; OR: odds ratio.

Histopathological examination. Pretreatment diagnosis was established by our pathologists using samples from core needle biopsy. The items investigated were the presence or absence of lymph node metastasis, nuclear grade, ER/PgR status, and HER2. Recent data suggest that several biological markers, especially Ki-67, may have the potential to predict the effectiveness of NAC with anthracycline and taxane. Therefore, we performed a post-hoc analysis of outcomes according to Ki-67. Immunostaining of ER, PgR, Ki-67, and HER2 was conducted as previously described (8). The positive cell rates for ER/PgR were determined by Immunohistochemistry. An assessment value of 10% or higher was rated as positive. Proliferative activity was determined by immunostaining for Ki-67 antibody (Dako, Tokyo, Japan). The fraction of proliferating cells was based on a count of at least 500 tumor cells. The Ki-67 values were expressed as the percentage of positive cells in each case.

Statistical analysis. The primary endpoint was the pCR rate of the treatment. Pathological response grades were stratified by tumor and nodal staging, patient age, and clinical response. Secondary endpoints included predictors for pCR, DFS, the rate of breast-conserving surgery, and safety. A 10-30% pCR rate was reported based on histopathology in preoperative anthracycline plus taxane (PTX) chemotherapy regimens. The required number of patients was calculated as 41, using a 25% expected efficacy rate, 10% threshold efficacy rate, two-sided alpha level of 0.05, and 80% power for the statistical analysis of the primary endpoint for this sequential combination chemotherapy. Analyses were performed with JMP (version 9; SAS Institute Inc., Tokyo, Japan).

Results

Patient characteristics. Between April 2004 and March 2007, 43 patients were prospectively enrolled. The characteristics of the study population are presented in Table II. The median age was 50 (range: 20-69) years. The majority of patients had T2 tumors.

Efficacy of NAC. The patients were evaluable regarding their response and toxicity. Clinical responses were rated as cCR in 9 patients (22%), cPR in 25 patients (59%), and cSD in 9 patients (19%). The pCR was seen in 25.6%. Breast-conserving surgery was achieved in 58% of all 43 patients. Furthermore, multiple logistic regression analysis was performed to examine factors including menopausal status, tumor size, ER status, PgR status, HER2 status, and clinical response (Table III). Multivariate analysis showed that the HER2 status was an independent predictive factor of pCR. The pCR rates stratified by HER2 and ER are shown in Figure 1. The pCR rate was 75%, 50%, 9% and 0 % in $HER2^+/ER^-$, $HER2^+/ER^+$, $HER2^-/ER^-$, and $HER2^-/ER^+$ patients, respectively.

The estimated 4-year DFS was 78% for all patients. Patients who achieved pCR did not show an improved DFS compared to those without pCR (log-rank test, $p<0.05$, Figure 2). Because of evidence that Ki-67 may be useful to evaluate the neoadjuvant setting (8, 9), we evaluated the influence of the Ki-67 status and pCR. This analysis should be regarded as exploratory, because it was not prespecified. As a result, the DFS rate of patients with lower (<15%) Ki-67 values was higher than that of patients with higher (≥15%) Ki-67 values.

The toxicities were manageable and the safety profile is summarized in Table IV. Dose reduction and interuptation due

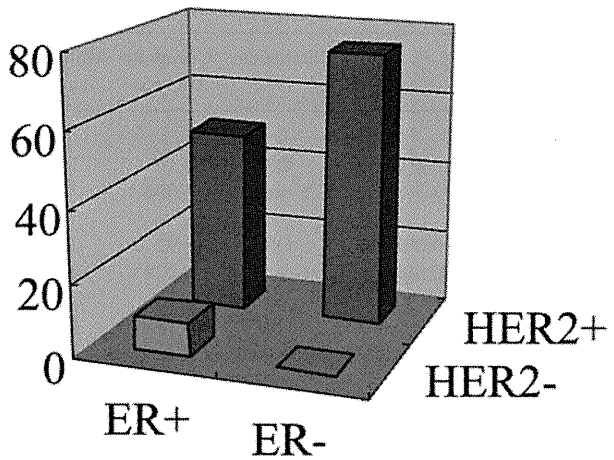

Figure 1. *Relationship between pCR and HER2/ER status.*

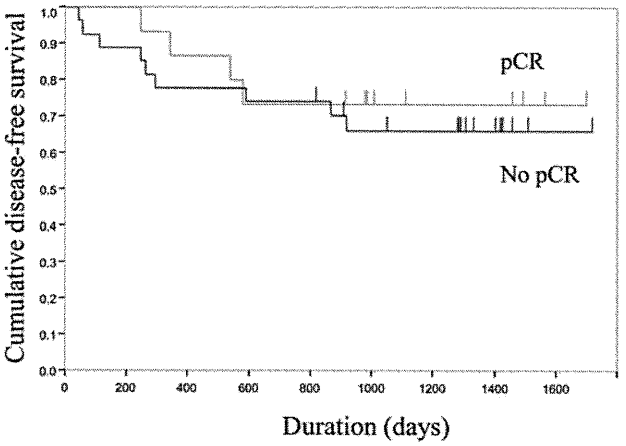

Figure 2. *Relationship of pCR and non-pCR to disease-free survival.*

to toxicities did not occur during treatment. The most common toxicity was nausea, which was observed in 62.8% of patients during DC treatment and 33% of patients during paclitaxel treatment. Grade 3-4 nausea was not seen in either treatment. Grade 3 neutropenia was reported in 2.3% and 7.1% of patients during treatment with DC and paclitaxel, respectively.

Table IV. *Treatment-related toxicities reported by patients in the study.*

	DC (N=43)		Paclitaxel (N=42)	
Toxicity	All grades	Grade 3+	All grades	Grade 3+
Neutropenia	17 (39.5%)	1 (2.3%)	17 (40.5%)	3 (7.1%)
Nausea	27 (62.8%)	0 (0.0%)	14 (33.3%)	0 (0.0%)
Vomiting	19 (44.2%)	0 (0.0%)	7 (16.7%)	0 (0.0%)
Hair loss	19 (44.2%)	0 (0.0%)	7 (16.7%)	0 (0.0%)
Stomatitis	8 (18.6%)	0 (0.0%)	1 (2.4%)	0 (0.0%)
Peripheral neuropathy	4 (9.3%)	0 (0.0%)	24 (57.1%)	2 (4.8%)
Subungual bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hand–foot syndrome	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)
Diarrhea	0 (0.0%)	0 (0.0%)	2 (4.8%)	0 (0.0%)

Discussion

Our study demonstrates that DC followed by paclitaxel is a promising NAC regimen for patients with breast cancer not amenable to conservative surgery. In other studies, the regimen of three cycles of 5-fluorouracil plus epirubicin plus cyclophosphamide followed by three cycles of docetaxel at 100 mg/m^2 led to the favorable result of an 18% risk reduction in DFS and 27% risk reduction in overall survival. However, in Japan, the standard dose of docetaxel is 75 mg/m^2. Therefore, we selected DC followed by weekly paclitaxel, and showed that the actual 4-year DFS rate of 78% was similar to the results of other studies (1-5). Unfortunately, there was no significant improvement in DFS regardless of the existence of pCR, possibly because this was not a large study. However, the DFS rate of patients with lower Ki-67 values (<15%) was higher than that of patients with higher values (≥15%).

Regarding toxicity, there were no severe toxic effects as compared with other recent studies (1-5). In terms of the incidence of febrile neutropenia, it was lower than that of other studies. (1-5). This confirms that DC followed by weekly paclitaxel as the neoadjuvant setting is appropriate for Japanese women.

In addition, we investigated ER, PgR, HER2, and Ki-67. We found that the pCR rate was the highest in patients who were ER$^-$/HER2$^+$. pCR was significantly associated with HER2 positivity based on multivariate analysis. Furthermore, in the present study, a higher pCR was often found in patients with tumors with a higher Ki-67 value, and there was no pathological responder in cases with Ki-67 <15% (data not shown). Regarding breast cancer subtypes, Ki-67 values were higher in patients with triple-negative tumors (10-13). These tumors respond more frequently to a neoadjuvant setting. On the other hand, ER$^+$ and/or PgR$^+$ tumors had lower Ki-67 values (10-13). These tumors respond more frequently to endocrine therapy. Therefore, clarifying the proliferative activity may be important for the treatment of breast cancer.

HER2 overexpression was suggested to be a predictor of the sensitivity to anthracycline chemotherapy (12). Indeed, in this study, HER2 was the only predictive factor for pCR. However, in the present study, trastuzumab was not administered to patients with HER2-overexpressing tumors because its use in such a setting has not yet been approved in

Japan. Recently, trastuzumab was found to significantly improve the prognosis and response to chemotherapy in such patients; the pCR rate was significantly higher in patients who were treated with trastuzumab (15-17). The relationship between HER2 overexpression and the response to chemotherapy with trastuzumab needs future investigation.

In conclusion, DC followed by weekly paclitaxel is safe, feasible, and effective as a preoperative adjuvant chemotherapy for Japanese women with breast cancer.

References

1 Kuerer HM, Newman LA, Smith TL Ames FC, Hunt KK, Dhingra K, Theriault RL, Singh G, Binkley SM, Sneige N, Buchholz TA, Ross MI, McNeese MD, Buzdar AU, Hortobagyi GN and Singletary SE: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol *17*: 460-469, 1999.

2 Kaufmann M, Hortobagyi GN, Goldhirsch A Scholl S, Makris A, Valagussa P, Blohmer JU, Eiermann W, Jackesz R, Jonat W, Lebeau A, Loibl S, Miller W, Seeber S, Semiglazov V, Smith R, Souchon R, Stearns V, Untch M and von Minckwitz G: Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol *24*: 1940-1949, 2006.

3 Bear HD, Anderson S, Smith RE, Geyer CE Jr., Mamounas EP, Fisher B, Brown AM, Robidoux A, Margolese R, Kahlenberg MS, Paik S, Soran A, Wickerham DL and Wolmark N: Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol *24*: 2019-27, 2006.

4 Abrial SC, Penault-Llorca F, Delva R, Bougnoux P, Leduc B, Mouret-Reynier MA, Mery-Mignard D, Bleuse JP, Dauplat J, Curé H and Chollet P: High prognostic significance of residual disease after neoadjuvant chemotherapy: a retrospective study in 710 patients with operable breast cancer. Breast Cancer Res Treat *94*: 255-263, 2005.

5 Toi M, Nakamura S, Kuroi K, Iwata H, Ohno S, Masuda N, Kusama M, Yamazaki K, Hisamatsu K, Sato Y, Kashiwaba M, Kaise H, Kurosumi M, Tsuda H, Akiyama F, Ohashi Y and Takatsuka Y: Phase II study of preoperative sequential FEC and docetaxel predicts of pathological response and disease-free survival. Breast Cancer Res Treat *110*: 531-539, 2008.

6 Kinoshita T: Preoperative therapy: recent findings. Breast Cancer *23*: 2010.

7 Iwase S, Yamamoto, D, Kitamura K, Odagiri H, Teramoto S, Ohtani S, Doi T, Kinebuchi K, Kuroda Y and NagumoY: Phase II study of AC (doxorubicin and cyclophosphamide) followed by weekly paclitaxel as neoadjuvant chemotherapy in operable patients with primary breast cancer. J Clin Oncol *27*: (suppl) abstr. e11587, 2009.

8 Nishimura R, Osako T, Okumura Y, Hayashi M and Arima N: Clinical significance of Ki-67 in neoadjuvant chemotherapy for primary breast cancer as a predictor for chemosensitivity and for prognosis. Breast Cancer *17*: 269-275, 2010.

9 von Minckwitz G, Sinn HP, Raab G, Loibl S, Blohmer JU, Eidtmann H, Hilfrich J, Merkle E, Jackisch C, Costa SD, Caputo A and Kaufmann M: Clinical response after two cycles compared to HER2, Ki-67, p53, and BCL-2 in independently predicting a pathological complete response after preoperative chemotherapy in patients with operable carcinoma of the breast. Breast Cancer Res *10*: R30, 2008.

10 Nishimura R and Arima N: Is triple negative a prognostic factor in breast cancer? Breast Cancer *15*: 303-308, 2008.

11 Nishimura R, Okumura Y and Arima N: Trastuzumab: monotherapy *versus* combination therapy for treating recurrent breast cancer – time to progression and survival. Breast Cancer *15*: 57-64, 2008.

12 Gennari A, Sormani MP, Pronzato P, Puntoni M, Colozza M, Pfeffer U and Bruzzi P: HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. J Natl Cancer Inst *100*: 14-20, 2008.

13 Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN and Pusztai L: Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol *26*: 1275-1281, 2008.

14 Di Leo A, Tanner M, Desmedt C, Paesmans M, Cardoso F, Durbecq V, Chan S, Perren T, Aapro M, Sotiriou C, Piccart MJ, Larsimont D and Isola J; TAX 303 Translational Study Team: *p53* gene mutations as a predictive marker in a population of advanced breast cancer patients randomly treated with doxorubicin or docetaxel in the context of a phase III clinical trial. Ann Oncol *18*: 997-1003, 2007.

15 Sánchez-Muñoz A, García-Tapiador AM, Martínez-Ortega E, Dueñas-García R, Jaén-Morago A, Ortega-Granados AL, Fernández-Navarro M, de la Torre-Cabrera C, Dueñas B, Rueda AI, Morales F, Ramírez-Torosa C, Martín-Salvago MD and Sánchez-Rovira P: Tumour molecular subtyping according to hormone receptors and HER2 status defines different pathological complete response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. Clin Transl Oncol *10*: 646-653, 2008.

16 Peintinger F, Buzdar AU, Kuerer HM, Mejia JA, Hatzis C, Gonzalez-Angulo AM, Pusztai L, Esteva FJ, Dawood SS, Green MC, Hortobagyi GN and Symmans WF: Hormone receptor status and pathologic response of HER2-positive breast cancer treated with neoadjuvant chemotherapy and trastuzumab. Ann Oncol *19*: 2020-2025, 2008.

17 Madarnas Y, Trudeau M, Franek JA, McCready D, Pritchard KI and Messersmith H: Adjuvant/neoadjuvant trastuzumab therapy in women with HER2/neu-overexpressing breast cancer: a systematic review. Cancer Treat Rev *34*: 539-557, 2008.

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研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Takeda T, Yamaguchi T, Yaegashi N.	Perceptions and attitudes ofJapanese gynecologic cancer patients to Kampo (Japanese herbal)medicines.	International Journal of Clinical Oncology		Epub ahead of print	2011

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http://www.biomedcentral.com/1471-2288/11/80

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Alternative statistical methods for estimating efficacy of interferon beta-1b for multiple sclerosis clinical trials

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Abstract

Background: In the randomized study of interferon beta-1b (IFN beta-1b) for multiple sclerosis (MS), it has usually been evaluated the simple annual relapse rate as the study endpoint. This study aimed to investigate the performance of various regression models using information regarding the time to each recurrent event and considering the MS specific data generation process, and to estimate the treatment effect of a MS clinical trial data.

Methods: We conducted a simulation study with consideration of the pathological characteristics of MS, and applied alternative efficacy estimation methods to real clinical trial data, including 5 extended Cox regression models for time-to-event analysis, a Poisson regression model and a Poisson regression model with Generalized Estimating Equations (GEE). We adjusted for other important covariates that may have affected the outcome.

Results: We compared the simulation results for each model. The hazard ratios of real data were estimated for each model including the effects of other covariates. The results (hazard ratios of high-dose to low-dose) of all models were approximately 0.7 (range, 0.613 - 0.769), whereas the annual relapse rate ratio was 0.714.

Conclusions: The precision of the treatment estimation was increased by application of the alternative models. This suggests that the use of alternative models that include recurrence event data may provide better analyses.

Background

Multiple sclerosis (MS) is the most common demyelinating disorder of the central nervous system, and is characterized by repeated episodes of neurological dysfunction with variable remission. Since 1993, the beneficial effects of interferon beta have been shown [1], and in Japan, interferon beta-1b (IFN beta-1b) has significantly reduced relapse rates and reduced MRI lesion areas in patients with relapsing-remitting MS [2]. Recently, Kappos et al. [3] reported that IFN beta-1b can delay the conversion to clinically definite MS. Carroll [4] performed a comprehensive review of clinical studies of MS therapies.

The long-term treatment effects for chronic recurrent diseases such as MS should be evaluated in clinical trials. In the past, the primary endpoint in clinical trials of MS has been the annual relapse rate, the change in a clinical indicator such as the Expanded Disability Status Scale (EDSS) score or total area of MS lesions on the MRI scan from entry time, the proportion of non-relapsed patients, or the time to the first recurrence [1,2,5-10]. Meanwhile, extended methods of survival analysis for time-to-event data have been proposed, and such methods are useful when study subjects experience 2 or more events. Considering the recurrent events in survival analysis should theoretically increase the estimation efficiency regarding the effects of treatment [11]. Although these methods have not generally been applied to MS clinical trial data, Wang et al. [12] recently examined some of the models. Excellent reviews are available regarding how these methods can contribute to the estimation of treatment effects [11,13,14]. When using these models, it is important to pay attention to the nature of the models because the results of the estimation are highly dependent on the clinical situation [15]. In real clinical studies, the concerned events might occur rarely, several events might occur simultaneously, or several events might occur separately with high correlation.

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Appropriate models should be selected after considering the relationship between the assumptions of the models and the manner in which the events occur. For example, if we analyse the disease data such that the deteriorations of many lesions are found simultaneously, we should select the model that can manage the count data approach rather than the gap time modeling of event history analysis.

In this study, we focused on the extended Cox proportional models and Poisson regression model using Generalized Estimating Equations (GEE), which can be analyzed using existing statistical packages such as SAS. Using these regression models, we can estimate the adjusted treatment effect while considering the important covariates that might affect the outcomes, whereas the relapse rates provide only non-adjusted estimate [16]. The objective of this study was to investigate the performance of these models through a simulation study with MS-specific data generation processes and to apply various models that are used for estimating the treatment effect to a real clinical trial data set. This data set comprises the effect of IFN beta-1b on MS with special attention to subjects with relapsing-remitting MS.

Methods

Subjects

A phase II randomized controlled clinical trial was conducted to compare the effect of 2 different doses (high-dose: 250 μg and low-dose: 50 μg) of IFN beta-1b on relapsing-remitting MS in Japan. Details of the trial design, inclusion criteria, baseline demographics, and efficacy results have been published [2]. In the trial, 205 patients with relapsing-remitting MS were randomized, and efficacy was assessed in 188 patients (55 male and 133 female patients). The primary endpoint of the study was the evaluation of the annual relapse rate. The percentage of patients who experienced a relapse more than once during follow-up was 55.8% (53/95) of patients in the high-dose group and 65.6% (61/93) of patients in the low-dose group. In these groups, the maximum number of relapses was 7, and the minimum,- 0, with a median of 1. The annual relapse rates in the high- and low-dose groups as estimated by the person-time method were 0.763 and 1.069, respectively (relapse rate ratio = 0.714; 95% CI 0.560- 0.910; p = 0.006).

Models

Various survival models used for analysis of recurrent event data and that handle clustered and multiple event data have been proposed. Let $\lambda_{ij}(t)$ be the hazard function of the jth recurrence of the ith subject at time t; $\lambda_{0j}(t)$ be the baseline hazard function of the jth recurrence at time t; $Y_{ij}(t)$ be the indicator variable for the jth recurrence of the ith subject at time t, which is 1 when the subject is at risk and under observation and 0 otherwise; $X_{ij}(t)$ be the jth covariate vector of the ith subject at time t; and βj be the parameter vector for the jth recurrence, which includes the treatment effect. When each recurrence is assumed to have common effect, we omit the subscript j. Schematic forms of the models are shown in Figure 1.

The first model to be considered is the ordinary time-to-first-event model, which is formulated with the Cox proportional hazard model (hereafter referred to as "time-to-first-event Cox model"). It handles only the time-to-first-event data and ignores the information of the second or more events. Hereafter, the models that can deal with this lack of information are shown.

Andersen and Gill [17] extended the Cox proportional hazard model in the counting process formation (AG model). A Poisson process in which, each counting process has independent increments is assumed so that multiple events within the same subjects are regarded independently. The hazard of subject i at time t is

$$\lambda_i(t) = Y_i(t)\lambda_0(t)\exp\{\mathbf{X}_i(t)'\boldsymbol{\beta}\}.$$

Although subjects who have once experienced an event are excluded from the risk set from that time in the usual Cox model, subjects who have experienced at least 1 event and are under observation can also be included in the risk set in the AG model. Because the baseline hazard is assumed to be common among subjects, this model ignores the individual differences and might be effective when the overall treatment effects are of interest.

Prentice, Williams, and Peterson [18] also extended the Cox model. They proposed the conditional model, which assumes that a subject is not at risk for the jth event until he/she has experienced the (j-1)th event, where $Y_{ij}(t)$ is 0 until the (j-1)th event and after which it becomes 1 (PWP model). In terms of the time scale, 2 models are used. One model measures from the entry time and is called the total time model (PWP-T model). The hazard of the jth recurrence of subject i at time t is

$$\lambda_{ij}(t) = Y_{ij}(t)\lambda_{0j}(t)\exp\{\mathbf{X}_i(t)'\boldsymbol{\beta}_j\}.$$

The other model resets the clock at every recurrence and is called the gap time model (PWP-G model). Assigning t_{j-1} as the time at which the (j-1)th event occurs, the hazard of the jth recurrence of subject i at time t is

$$\lambda_{ij}(t) = Y_{ij}(t)\lambda_{0j}(t - t_{j-1})\exp\{\mathbf{X}_i(t)'\boldsymbol{\beta}_j\}.$$

Although the PWP model makes the interpretation easy, the sizes of the risk sets become relatively small as the number of events increases, making the estimates unstable.

Wei, Lin, and Weissfeld [19] modeled the marginal distribution of the time of each occurrence of the event

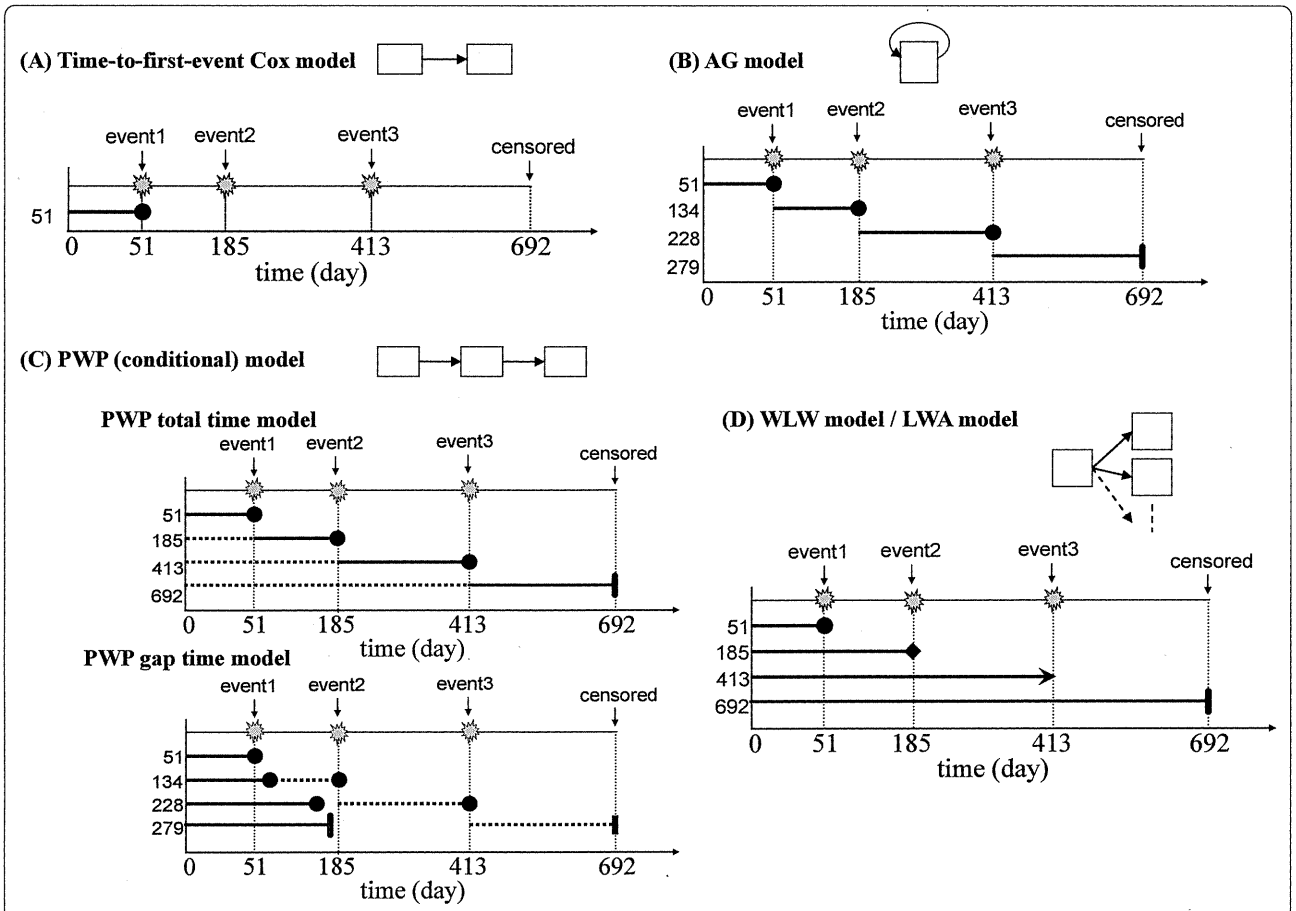

Figure 1 Schematic forms of the various extended time-to-event Cox regression models. Each arrow represents a stratum. Arrow diagrams describe about the behavior of ID = 1 in the sample data (DATA = MS) in Appendix (Additional file 1), who experiences the first event at day 51, second event at day 185, third event at day 413 and finally have censored at day 692. (A) "Time-to-first-event Cox model" only uses the information of the time to first event (the day 51). (B) "AG model" shows the renewal process of the events. (C) "PWP model" shows how the conditional models are constructed. (D) "WLW model" and "LWA model" model the marginal distribution of each event occurrence time.

using the Cox model (WLW model). The hazard of the jth recurrence of subject i at time t is

$$\lambda_{ij}(t) = Y_{ij}(t)\lambda_{0j}(t)\exp\{\mathbf{X}_i(t)'\boldsymbol{\beta}_j\}.$$

In this model, each recurrence is modeled as a separate stratum, and each subject appears in all of the strata so that no assumptions are made with respect to the recurrence process. However, this may result in substantial efficiency loss because it ignores the obvious dependency structure, in that the $(j+1)$th recurrent time must exceed the jth.

On the other hand, Lee, Wei, and Amato [20] proposed a model (LWA model) that assumes a common baseline hazard, where the hazard can be written as

$$\lambda_{ij}(t) = Y_{ij}(t)\lambda_0(t)\exp\{\mathbf{X}_i(t)'\boldsymbol{\beta}_j\}.$$

The same subjects can enter several risk sets simultaneously, although its unnaturalness is discussed at the same time.

In terms of the inference of the parameter vector, the use of robust variance, which can handle intra-subject correlations, is considered to be desirable for all models described above (AG, PWP, WLW, and LWA models). Regarding the parameter estimation of the PWP, WLW, and LWA models, each recurrence is assumed to have a common effect in this study.

The Poisson regression model fits the framework of the generalized linear models in which, the response variable, which is the number of occurrences of the event in a fixed time interval, follows Poisson distribution. Let $\mu(\mathbf{X})$ be the expected value of the number of relapses; $N(\mathbf{X})$, the total observation period; $\lambda(\mathrm{X})$, the constant relapse rate of MS; X, the covariate vector; and β, the parameter vector to be estimated. The relapse rate can then be written as

$$\log\{\lambda(\mathbf{X})\} = \log\left\{\frac{\mu(\mathbf{X})}{N(\mathbf{X})}\right\} = \mathbf{X}'\boldsymbol{\beta}.$$

Thus, $\mu(\mathbf{X}) = N(\mathbf{X})\exp(\mathbf{X}'\boldsymbol{\beta})$.

The relapse rate is not necessarily constant throughout the observation period; it is better to partition the time axis into intervals of constant rates.

Consequently, the intra-subject correlation of the relapse rate among the intervals can be discussed in terms of GEE. GEE is an extension of generalized linear models and regards a subject as a cluster so that the treatment effect can be estimated considering the correlation structure among response variables [21]. It is expected to be a flexible method for analyzing recurrent event data because it can be used even if many of the aforementioned assumptions regarding the proportional hazard models do not hold. In this study, the GEE-Poisson model was applied, and intervals were set at 6 months, each with the common rate.

Simulation study

To determine which model is the most suitable for analyzing MS clinical trial data, we conducted the simulation study with consideration of the disease progression process or natural history. When performing a simulation study, we should examine the event generation process, which might be suited to the situation of the disease progression process [22]. The data generation process of this study was as follows. In a hypothetical randomized controlled clinical trial with placebo (n = 100) and active (n = 100) groups, we assumed that each patient had 10 hypothetical latent lesions in their brain and that the lesions were in the inactive phase at the entry time. The recurrence time was recorded after each lesion developed to the active phase. This setting modeled some MS pathological characteristics, such as time and spatial distribution of the lesions. The total follow-up period was set to 3 years, and the censoring time, which was assumed to be independent from the recurrence time, was generated using a Weibull distribution $S(t) = \exp(-\lambda t^{\gamma})$ with the shape parameter $\gamma = 2.1399$ and the scale parameter $\lambda = 0.000000576$. The time to recurrence was also generated using a Weibull distribution, and 2 different scenarios were considered.

Scenario 1: All patients have individual identical Weibull distribution parameters, $\gamma = 1.1452$ and $\lambda = 0.00141$.

Scenario 2: Mixture population of 3 different sets of parameters; 46% of the population has $\gamma = 1.2442$ and $\lambda = 0.000604$, 45% of the population has $\gamma = 1.1550$ and $\lambda = 0.001578$, and 9% of the population has $\gamma = 1.9694$ and $\lambda = 0.0000661$.

The parameters used in our simulation study were calculated from other clinical trial data in Japan [23], especially for the placebo group, which can be regarded as the natural history cohort [24]. The mixture proportions described in Scenario 2 were obtained from the distribution of the number of recurrences in the year preceding the study, which was one of the important covariates. The hazard ratio (relapse rate ratio) of the active group to the placebo group was set at 1/1.3, such the true value of the Cox regression parameter (log-hazard ratio) was log(1/1.3) = -0.26236. Each simulation was repeated 1000 times, and the results were evaluated via the bias and mean square error (MSE). The bias is the difference between the estimated and true (or reference) values; thus, the treatment effect would be underestimated if we obtained positive bias and, overestimated if we obtained negative bias. The MSE considers both bias and variability as gauged by the variance of parameter estimates.

After the simulation study, the models were applied to the IFN beta real clinical trial data separately. All statistical analyses, including the simulation study, were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The SAS sample programs for the use of these models are shown in the appendix of this article (Additional file 1), and a dummy data set is used to clarify the use of the models.

Results

The results of the simulation study are presented in Table 1. AG, Poisson, and GEE-Poisson models showed similar results, with positive bias and relatively small MSE in both scenarios. Almost no bias was detected in PWP-T, PWP-G, and LWA models in Scenario 1, whereas they showed larger bias in Scenario 2. In the WLW model, a relatively large bias with a negative direction was noted, indicating that an overestimation of the treatment effect and a large MSE were detected in both scenarios.

The various aforementioned models were then applied to the real clinical trial data introduced in the Methods section with adjustment for some important covariates, such as sex, age, EDSS score at entry time, total area of MS lesions on the MRI scan at the entry time, and number of recurrences in the year preceding the study. Table 2 shows the results of the analysis. The hazard ratio indicates the relative risk of the high-dose group to

Table 1 Bias and MSE from the simulation study

Models	[Scenario 1]		[Scenario 2]	
	Bias	MSE	Bias	MSE
1: Time-to-first-event Cox regression	-0.002	0.049	0.023	0.046
2: AG model	0.044	0.014	0.090	0.030
3-1: PWP-T model	-0.001	0.018	0.080	0.022
3-2: PWP-G model	0.007	0.017	0.101	0.029
4: WLW model	-0.162	0.076	-0.064	0.064
5: LWA model	0.001	0.017	0.046	0.037
6: Poisson regression model	0.044	0.016	0.090	0.026
7: GEE-Poisson model	0.046	0.014	0.088	0.030

Table 2 Estimates of treatment effects for MS clinical trials in Japan

Models	Parameter Estimates	Standard Error	Hazard Ratio [95%CI]	P value
1: Time-to-first-event Cox regression	-0.263	0.194	0.769 [0.526, 1.123]	0.174
2: AG model	-0.377	0.170	0.686 [0.492, 0.957]	0.027
3-1: PWP-T model	-0.268	0.132	0.765 [0.591, 0.989]	0.041
3-2: PWP-G model	-0.306	0.135	0.736 [0.565, 0.960]	0.024
4: WLW model	-0.489	0.231	0.613 [0.390, 0.965]	0.035
5: LWA model	-0.427	0.195	0.653 [0.445, 0.957]	0.029
6: Poisson regression model	-0.371	0.171	0.690 [0.493, 0.965]	0.030
7: GEE-Poisson model	-0.352	0.169	0.703 [0.505, 0.980]	0.037

the low-dose group, and it is distributed from 0.613 (WLW model) to 0.769 (time-to-first-event Cox model). All models except the time-to-first-event Cox model showed a significant effect of high-dose IFN beta-1b. The standard error of the WLW model was the largest, while the PWP-T and PWP-G models showed relatively small values. The width of the confidence intervals of the AG, PWP-T, PWP-G, WLW, LWA, Poisson, and GEE-Poisson models was smaller than that of the time-to-first-event Cox model.

Regarding the behavior of the other covariates besides the IFN beta-1b variable, "the number of recurrences in the year preceding the study" showed significant differences in all 8 models. As the number increased, the hazard of recurrence in the study increased (range of hazard ratio among the 8 models: 1.164-1.375).

Discussion

Because MS is a heterogeneous disease with a variety of subtypes and transitional cases, it is not easy to evaluate drug efficacy. By conducting a simulation study and applying it to real clinical trial data, we examined various extended Cox regression models and a Poisson regression model using GEE, which can handle recurrent events - not only the number of recurrences or the time to the first event, but all recurrences that occurred during the follow-up period. With the use of the extended models, significant effects were detected and the importance of utilizing more than 1 recurrent time was suggested by our analyses.

From the simulation study results, treatment effect was relatively overestimated in the WLW model. The same tendency was observed in the analysis of the real data; the WLW model showed the smallest hazard ratio. This overestimation tendency might not be desirable, especially in confirmatory trials. The bias and MSE of the LWA model in Scenario 1 were small for homogeneous population because of the similarity of the assumption of the data generation process; however, in Scenario 2, both bias and MSE became larger to some extent for heterogeneous population. In terms of MSE of the PWP-T and PWP-G models, totally preferable results were obtained, but the bias differences between Scenarios 1 and 2 for each model were approximately 2 times larger than those of the other models; this finding suggests of possible unstable features in the PWP models. For the time-to-first-event Cox model, AG model, Poisson regression model, and GEE-Poisson model, no extreme differences were found.

We are then left to select the best model for our data. All models have their own assumptions and characteristics, and so, our decision must consider the nature and system of disease progression that we have analyzed in advance in order to make the correct choice. When we consider the pathological condition in MS, such as the time and spatial distribution of latent lesions, the LWA model seems to be reasonable because of the assumption of a common baseline hazard, which means that each latent lesion has the same risk of development. If we can assume that all subjects have the same number of lesions that can develop at the same risk, the LWA model becomes conceivable. In the same way, if we can assume that all subjects have the same number of lesions that can develop at different risks, the WLW model seems to be best fitted. However, such settings would be unrealistic. In addition, the precision of the estimates in the WLW and LWA models is relatively poor. As the number of lesions increases, the number of strata also increases, which might lead to unstable estimates.

If we assume that the independent increments for all events are even among subjects, then the AG model is reasonable; however, this assumption would be unnatural in this case. PWP models would involve a similar situation despite small standard errors. In fact, the martingale residuals, which enabled us to examine the increment dependency, showed negative slopes throughout the period. This suggests that the assumptions that the AG and PWP models required would not exactly hold. The estimates of the Poisson regression and GEE-Poisson models were quite similar, so the advantage of using the GEE-Poisson model was not entirely clear in our study. However, if we had had a longer follow-up period and more time intervals, the method that accounts for the intra-subject correlation structure among intervals would be the more attractive model.

Realistically speaking, the assumptions needed in the extended Cox regression models (AG, PWP, WLW, and LWA models) would be difficult to be completely examined because of the uncertainty of MS pathological and/or clinical deterioration mechanisms and that fact that no one can prove the correctness of these assumptions. The Poisson regression and GEE-Poisson models are free of such assumptions. Moreover, in terms of the advanced nature regarding consideration of intra-subject correlation for recurrences in the GEE-Poisson model, the GEE-Poisson model is preferred over the Poisson regression model. However, further study regarding the behavioral characterization among these models is still needed.

Conclusions

Our results indicate that the use of alternative models that include recurrence event data, especially the GEE-Poisson model, may provide better analysis for estimating the treatment effect.

Additional material

Additional file 1: Appendix: SAS programming codes (example). The SAS sample programs for the use of the regression models shown in this study are provided using a dummy data set.

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Authors' contributions

MNM, TY and YO participated in the design of the study. MNM performed the statistical analysis and drafted the manuscript. All the authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

1. The IFNB Multiple Sclerosis Study Group: **Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial.** *Neurology* 1993, **43**:655-661.
2. Saida T, Tashiro K, Itoyama Y, Sato T, Ohashi Y, Zhao Z: **Interferon beta-1b is effective in Japanese RRMS patients: a randomized, multicenter study.** *Neurology* 2005, **64**:621-630.
3. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, Montalban X, Bauer L, Jakobs P, Pohl C, Sandbrink R: **Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes.** *Neurology* 2006, **67**:1242-1249.
4. Carroll WM: **Clinical trials of multiple sclerosis therapies: improvements to demonstrate long-term patient benefit.** *Mult Scler* 2009, **15**:951-958.
5. The PRISMS Study Group: **Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis.** *Lancet* 1998, **352**:1498-1504.
6. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, Schiffer RB: **Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial.** *Neurology* 1995, **45**:1268-1276.
7. Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B: **Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis.** *Lancet* 1997, **349**:589-593.
8. Sorensen PS, Wanscher B, Jensen CV, Schreiber K, Blinkenberg M, Ravnborg M, Kirsmeier H, Larsen VA, Lee ML: **Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis.** *Neurology* 1998, **50**:1273-1281.
9. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group: **TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study.** *Neurology* 1999, **53**:457-465.
10. Miller DH, Kahn OA, Sheremata WA, Blumhardt LD, Rive GP, Libonati MA, Willmer-Hulme AJ, Dalton CM, Miszkiel KA, O'Connor PW: **A controlled trial of natalizumab for relapsing multiple sclerosis.** *N Engl J Med* 2003, **348**:15-23.
11. Therneau TM, Grambsch PM: *Modeling Survival Data: Extending the Cox Model* New York: Springer-Verlag; 2000.
12. Wang YC, Meyerson L, Tang YQ, Qian N: **Statistical methods for the analysis of relapse data in MS clinical trials.** *J Neurol Sci* 2009, **285**:206-211.
13. Yamaguchi T: **Recurrent event data analysis: A review.** *Japanese Journal of Biometrics* 2005, **26**:81-117.
14. Cook RJ, Lawless JF: *The Statistical Analysis of Recurrent Events* New York: Springer; 2007.
15. Kuramoto L, Sobolev BG, Donaldson MG: **On reporting results from randomized controlled trials with recurrent events.** *BMC Medical Research Methodology* 2008, **8**:35.
16. Klein JP, Moeschberger ML: *Survival Analysis: Techniques for Censored and Truncated Data.* 2 edition. New York: Springer; 2003.
17. Andersen PK, Gill RD: **Cox's regression model for counting processes: a large sample study.** *Ann Stat* 1982, **10**:1100-1120.
18. Prentice RL, Williams BJ, Peterson AV: **On the regression analysis of multivariate failure time data.** *Biometrika* 1981, **68**:373-379.
19. Wei LJ, Lin DY, Weissfeld L: **Regression analysis of multivariate incomplete failure time data by modeling marginal distributions.** *J Am Stat Assoc* 1989, **84**:1065-1073.
20. Lee EW, Wei LJ, Amato DA: **Cox-type regression analysis for large numbers of small groups of correlated failure time observations.** *Survival Analysis: State of the Art* 1992, 237-247.
21. Liang KY, Zeger SL: **Longitudinal data analysis using generalized linear models.** *Biometrika* 1986, **73**:13-22.
22. Metcalfe C, Thompson SG: **The importance of varying the event generation process in simulation studies of statistical methods for recurrent events.** *Stat Med* 2006, **25**:165-179.
23. Saida T, Ohashi Y, Tashiro K, Itoyama Y, Sato T, Hamaguchi K, Nishitani H, Shibasaki H, Araki S, Research committee for treatment of multiple sclerosis (Chairman: Igata A): **Treatment of multiple sclerosis with mizoribine: (1) clinical results of a double-blind, placebo-controlled study.** *Neuroimmunology* 1998, **6**:160-161.
24. Wingerchuk DM, Weinshenker BG: **The natural history of multiple sclerosis: implications for trial design.** *Curr Opin Neurol* 1999, **12**:345-349.

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ORIGINAL ARTICLE

Perceptions and attitudes of Japanese gynecologic cancer patients to Kampo (Japanese herbal) medicines

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Abstract
Background Kampo (Japanese herbal) medicine is the complementary and alternative medicine that is most frequently used by Japanese doctors. We studied the perceptions and attitudes of Japanese gynecologic cancer patients to Kampo medicines and analyzed the characteristics of the backgrounds of Kampo users.
Methods A total of 476 patients with gynecologic cancer completed a self-reported questionnaire on Kampo medicine. State anxiety and trait anxiety were also assessed using the State-Trait Anxiety Inventory.
Results It was confirmed that 22.9% of the women had used Kampo medicine. Kampo users were more likely to have had chemotherapy and were more likely to have experienced uncomfortable side effects of cancer treatment. Kampo users were more likely to believe that 'Kampo offers relief of symptoms,' 'fewer side effects than Western-style medicine,' and 'is not less effective than Western-style medicine' than nonusers. Kampo users expressed a stronger attitude of 'I want to take Kampo medicine.' Multiple risk ratio regression analysis revealed that chemotherapy (RR, 1.82; 95% CI, 1.14–2.91), lower state anxiety (RR, 0.76; 95% CI, 0.58–1.00), and higher trait anxiety (RR, 1.46; 95% CI, 1.11–1.92) were independently associated with Kampo use.
Conclusions This study showed that slightly less than one-fourth of Japanese gynecologic cancer patients take Kampo medicine. Kampo users made more favorable comments on Kampo medicine than nonusers. Our findings suggest that the psychological characteristics of individual patients is one of the factors that can influence the usage of Kampo.

Keywords Health survey · Anxiety · Complementary and alternative medicine · Japan

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Introduction

Complementary and alternative medicine (CAM) has been widely used throughout the world [1]. CAM is defined as a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional Western medicine. In spite of the lack of adequate clinical trials, CAM is used by an increasing number of cancer patients in developed countries, including Japan [2–4].

Japanese herbal medicine (Kampo) is derived from Chinese traditional medicine, which was introduced from China in the fifth to sixth centuries and greatly modified over a long period in Japan. Currently, 148 Kampo drugs (formulae) are covered by national health insurance. These Kampo formulae are available as extracted powder manufactured by drug makers, so we can prescribe them conveniently, just like a Western-style powder. In this situation, Kampo medicine is the CAM that is most frequently used

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by Japanese doctors. It has been reported that almost all doctors practicing CAM are Kampo practitioners (96%) [5]. Kampo is the most common type of CAM in Japan [6].

There are many reports about CAM and cancer patients in several countries, including Japan [2–4]. However, there has been no report about Kampo medicine and cancer patients. In this study, we have investigated the beliefs and attitudes about Kampo medicine among Japanese gynecologic cancer patients and analyzed the characteristics of backgrounds of Kampo users.

Methods

The study was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Study population

A cross-sectional study was conducted from December 2008 to March 2009. Data were collected from a sample of gynecologic cancer patients who were treated and followed at Tohoku University Hospital in Sendai, Japan. They were all diagnosed with invasive cancer by pathological examination. At a gynecology follow-up clinic, we recruited Japanese women who could complete a questionnaire themselves and were able to provide informed consent.

Questionnaire

The questionnaires consisted of three parts. The first part included general profile factors such as age, time from diagnosis to screening, cancer site, type of conventional treatment, and type of alternative treatment (Kampo medicine, dietary supplements). It has been reported that dietary supplements are as popular as Kampo medicine in Japan [6]. Therefore, we studied the usage of not only Kampo medicine but also of dietary supplements. The Kampo users included both those who were prescribed Kampo medicine by the doctors and those who bought Kampo medicine by themselves in a drugstore. We also asked about uncomfortable side effects of cancer treatment and satisfaction with conventional treatment on five-grade scales. The second part included an 8-item questionnaire concerning beliefs and attitudes about Kampo medicine with five-grade scales: 'It will be good for cancer treatment,' 'It will offer relief of symptoms,' 'It requires many days to be effective,' 'It has fewer side effects than Western-style medicine,' 'It is hard to take orally,' 'I want to take Kampo medicine,' 'It is less effective than Western-style medicine,' and 'It will relieve the side effects of Western-style medicine'. The third part was the Japanese edition of the State-Trait Anxiety Inventory (STAI) (Jitsumu-Kyoiku, Tokyo, Japan). STAI can evaluate state anxiety and trait anxiety and has been well validated [7, 8]. State anxiety means 'how anxious a patient feels at the time of the test' and trait anxiety means 'how anxious a patient generally feels.' It consists of two separate sets of 20-item self-rated 4-point scales. Higher scores reflect a greater degree of anxiety.

Analysis

The significance of differences between Kampo users and nonusers was evaluated by Chi-square test or the Mann–Whitney U test. To evaluate the contribution of Kampo users or nonusers, univariate and multivariate risk ratios of the individual characteristics were calculated. Statistical analysis was performed using Excel 2003 (Microsoft) with the add-in software Statcel 2 (OMS, Tokyo, Japan) and SAS Ver.9.1.3. (SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$.

Results

General profile

First, we analyzed the questionnaire results for part 1 and part 2. A total of 476 women completed the questionnaire. Fifty-six were dropped from the analysis because of incomplete data. Demographic and clinical characteristics are shown in Table 1. Eight women overlapped as to cancer site. All patients received at least one treatment. Among them, 96 women (22.9%) had taken Kampo medicine. In total, 46.9% of the women had used either Kampo medicine or dietary supplements.

Beliefs and attitudes about Kampo medicine

As shown in Table 2, the patients made favorable comments about Kampo medicine in general. More than 50% of the women responded with 'fairly true' or 'very true' to the questionnaire statements 'It will be good for cancer treatment,' 'It will offer relief of symptoms,' 'It has fewer side effects than Western-style medicine,' and 'It will relieve the side effects of Western-style medicine.'

Comparison of Kampo users and nonusers in beliefs and attitudes about Kampo medicine

With regard to the difference in demographic and clinical characteristics between Kampo users and nonusers, there was no significant difference in age, time from diagnosis to screening, cancer site, and satisfaction with conventional treatment (see Table 1). Kampo users were more likely to

Table 1 Demographic and clinical characteristics

Demographic/clinical characteristics	Total (%) $n = 420$	Kampo users (%) $n = 96$	Nonusers (%) $n = 324$	P
Age (years) median [range]	53 [19–76]	55 [19–76]	53 [22–76]	0.162 (Student's t test)
Time from diagnosis to screening (years)				
<1	112 (26.7)	28 (29.2)	84 (25.9)	0.332 (Chi-square test)
1–2	94 (22.4)	20 (20.8)	74 (22.8)	
2–3	74 (17.6)	18 (18.8)	56 (17.3)	
3–4	44 (10.5)	7 (7.29)	37 (11.4)	
4–5	42 (10.0)	6 (6.25)	36 (11.1)	
>5	54 (12.9)	17 (17.7)	37 (11.4)	
Cancer site				
Cervix	107 (25.5)	21 (21.9)	86 (26.5)	0.357
Corpus	156 (37.1)	34 (35.4)	122 (37.7)	0.690
Ovary	119 (28.3)	33 (34.4)	86 (26.5)	0.135
Other	41 (9.8)	8 (8.3)	33 (10.2)	0.591
Unknown	5 (1.2)	2 (2.1)	3 (0.9)	0.358 (Chi-square test)
Treatment				
Operation	381 (90.7)	88 (91.7)	293 (90.4)	0.714
Chemotherapy	256 (61.0)	69 (71.9)	187 (57.7)	0.013
Radiotherapy	78 (18.6)	20 (20.8)	58 (17.9)	0.516 (Chi-square test)
Alternative treatment				
Kampo	96 (22.9)			
Dietary supplements	130 (31.0)			
Kampo or dietary supplements	197 (46.9)			
Uncomfortable side effects of cancer treatment				
1 = not at all	61 (14.5)	13 (13.5)	48 (14.8)	0.002 (Mann–Whitney U test)
2 = mild	70 (16.7)	8 (8.3)	62 (19.1)	
3 = moderate	61 (14.5)	11(11.5)	50 (15.4)	
4 = severe	126 (30.0)	28 (29.2)	98 (30.2)	
5 = very severe	102 (24.3)	36 (37.5)	66 (20.4)	
Satisfaction with conventional treatment				
1 = highly unsatisfied	7 (1.7)	2 (2.0)	5 (1.5)	0.185 (Mann–Whitney U test)
2 = unsatisfied	16 (3.8)	4 (4.1)	12 (3.7)	
3 = neither unsatisfied nor satisfied	144 (34.3)	21 (21.9)	123 (38.0)	
4 = satisfied	148 (35.2)	47 (49.0)	101 (31.2)	
5 = highly satisfied	105 (25.0)	22 (22.9)	83 (25.6)	

have had chemotherapy (71.9% vs. 57.7%; $P = 0.013$ by chi-square test) and were more likely to have felt uncomfortable side effects of cancer treatment ($P = 0.002$ by Mann–Whitney U test). Next, we analyzed the difference of beliefs and attitudes about Kampo medicine between Kampo users and nonusers. As shown in Table 3, Kampo users made more favorable comments about Kampo medicine than nonusers. Kampo users were more likely to believe that 'Kampo medicine will offer relief of symptoms,' 'Kampo medicine has fewer side effects than

Table 2 Beliefs and attitudes about Kampo medicine

Beliefs and attitudes	Not true at all 1	Somewhat not true 2	Neither true nor untrue 3	Fairly true 4	Very true 5
It will be good for cancer treatment	8 (1.9)	37 (8.8)	149 (35.5)	190 (45.2)	36 (8.6)
It will offer relief of symptoms	3 (0.7)	29 (6.9)	101 (24.0)	249 (59.3)	38 (9.0)
It requires many days to be effective	4 (1.0)	23 (5.5)	68 (16.2)	218 (51.9)	107 (25.5)
It has fewer side effects than Western-style medicine	6 (1.4)	16 (3.8)	81 (19.3)	224 (53.3)	93 (22.1)
It is hard to take orally	28 (6.7)	69 (16.4)	121 (28.8)	145 (34.5)	57 (13.6)
I want to take Kampo medicine	21 (5.0)	49 (11.7)	195 (46.4)	105 (25.0)	50 (11.9)
It is less effective than Western-style medicine	16 (3.8)	101 (24.0)	203 (48.3)	95 (22.6)	5 (1.2)
It will relieve the side effects of Western-style medicine	10 (2.4)	26 (6.2)	167 (39.8)	184 (43.8)	33 (7.9)

Values in parentheses are expressed in percentage

Table 3 Beliefs and attitudes about Kampo medicine: Kampo user versus non-user

Beliefs and attitudes	Not true at all 1	Somewhat not true 2	Neither true nor untrue 3	Fairly true 4	Very true 5	*P* (Mann–Whitney *U* test)
It will be good for cancer treatment	1	12	32	43	8	0.702
	7	25	117	147	28	
It will offer relief of symptoms	1	6	12	66	11	0.011
	2	23	89	183	27	
It requires many days to be effective	2	9	11	53	21	0.382
	2	14	57	165	86	
It has fewer side effects than Western-style medicine	2	3	9	56	26	0.021
	4	13	72	168	67	
It is hard to take orally	15	19	15	37	10	0.084
	13	50	106	108	47	
I want to take Kampo medicine	4	6	21	32	33	<0.001
	17	43	174	73	17	
It is less effective than Western-style medicine	7	36	33	20	0	0.001
	9	65	170	75	5	
It will relieve the side effects of Western-style medicine	4	7	33	42	10	0.686
	6	19	134	142	23	

Upper line, Kampo user ($n = 96$); lower line, Kampo nonuser ($n = 324$)

Western-style medicine,' and 'Kampo medicine is not less effective than Western-style medicine' than were nonusers. Kampo users expressed a stronger attitude of 'I want to take Kampo medicine.'

Comparison of anxiety in Kampo users and nonusers

In combination with the questionnaire concerning the beliefs and attitudes about Kampo medicine, we have assessed the anxiety using STAI. Among the 420 women who completed parts 1 and 2 of the questionnaire, 321 women completed STAI (Table 4). The average scores of state anxiety in Kampo users ($n = 72$) and nonusers ($n = 249$) were 46.8 (range, 21–72), and 46.3 (range, 20–80), respectively. The trait anxiety scores in Kampo users and nonusers were 50.8 (range, 20–72) and 48.3 (range, 24–80), respectively. There were no significant differences in STAI scores between Kampo users and nonusers. Other demographic and clinical characteristics are also shown in Table 4. Seven women overlapped as to cancer site. With regard to the difference in demographic and clinical characteristics between Kampo users and

Table 4 Demographic and clinical characteristics of patients who completed the State-Trait Anxiety Inventory (STAI)

Demographic/clinical characteristics	Total (%) $n = 321$	Kampo users (%) $n = 72$	Nonusers (%) $n = 249$	P
State anxiety average [range]	46.4 [20–80]	46.8 [21–72]	46.3 [20–80]	0.742 (Student's t test)
Trait anxiety average [range]	48.9 [20–80]	50.8 [20–72]	48.3 [24–80]	0.087 (Student's t test)
Age (years) median [range]	51 [19–75]	50 [19–75]	51 [22–75]	0.526 (Student's t test)
Time from diagnosis to screening (years)				
<1	84 (26.1)	20 (27.8)	64 (25.7)	0.494 (Chi-square test)
1–2	76 (23.7)	17 (23.6)	59 (23.7)	
2–3	57 (17.8)	13 (18.1)	44 (17.7)	
3–4	34 (10.6)	5 (6.9)	29 (11.7)	
4–5	33 (10.3)	5 (6.9)	28 (11.2)	
>5	37 (11.5)	12 (16.7)	25 (10.0)	
Cancer site				
Cervix	82 (25.5)	17 (23.6)	65 (26.1)	0.669
Corpus	110 (34.3)	22 (30.6)	88 (35.3)	0.451
Ovary	96 (29.9)	27 (37.5)	69 (27.7)	0.110
Other	36 (11.2)	6 (8.3)	30 (12.1)	0.379
Unknown	4 (1.2)	1 (1.4)	3 (1.2)	0.494 (Chi-square test)
Treatment				
Operation	292 (91.0)	66 (91.7)	226 (90.8)	0.814
Chemotherapy	197 (61.4)	53 (73.6)	144 (57.8)	0.015
Radiotherapy	56 (17.4)	17 (23.6)	39 (15.7)	0.118 (Chi-square test)
Alternative treatment				
Kampo	72 (22.4)			
Dietary supplements	101 (31.5)			
Kampo or dietary supplements	147 (45.8)			
Uncomfortable side effects of cancer treatment				
1 = not at all	42 (13.1)	10 (13.9)	32 (12.9)	0.020 (Mann–Whitney U test)
2 = mild	48 (15.0)	3 (4.2)	45 (18.1)	
3 = moderate	47 (14.6)	10 (13.9)	37 (14.9)	
4 = severe	101 (31.5)	23 (31.9)	78 (31.3)	
5 = very severe	83 (25.9)	26 (36.1)	57 (22.9)	
Satisfaction with conventional treatment				
1 = highly unsatisfied	5 (1.6)	1 (1.4)	4(1.6)	0.176 (Mann–Whitney U test)
2 = unsatisfied	11 (3.4)	2 (2.8)	9 (3.6)	
3 = neither unsatisfied nor satisfied	122 (38.0)	19 (26.4)	103 (41.4)	
4 = satisfied	111 (34.6)	36 (50.0)	75 (30.1)	
5 = highly satisfied	72 (22.4)	14 (19.4)	58 (23.3)	

nonusers, there was no significant difference in age, time from diagnosis to screening, cancer site, and satisfaction with conventional treatment. Kampo users were more likely to have had chemotherapy and were more likely to have felt uncomfortable side effects of cancer treatment. These results were essentially same as shown in Table 1.

Table 5 Risk ratio of predictors for Kampo use

Demographic/clinical characteristics	Univariate			Multivariate		
	Risk ratio	95% CI	*P*	Risk ratio	95% CI	*P*
Age	1.06	0.88–1.28	0.520			
Time from diagnosis to screening	1.01	0.89–1.14	0.910			
Cancer site						
Cervix	0.90	0.56–1.46	0.677			
Corpus	0.84	0.54–1.32	0.460			
Ovary	1.41	0.93–2.14	0.103			
Other	0.72	0.34–1.54	0.399			
Treatment						
Operation	1.09	0.52–2.30	0.816			
Chemotherapy	1.76	1.09–2.82	0.020	1.82	1.14–2.91	0.012
Radiotherapy	1.46	0.92–2.32	0.106			
Dietary supplements	1.23	0.81–1.87	0.331			
Uncomfortable side effects of cancer treatment	1.20	1.02–1.42	0.032			
Satisfaction with conventional treatment	1.13	0.91–1.42	0.274			
State anxiety	1.03	0.86–1.24	0.748	0.76	0.58–1.00	0.050
Trait anxiety	1.17	0.98–1.39	0.089	1.46	1.11–1.92	0.007

CI confidence interval

Characteristics associated with use of Kampo

Using the data of the 321 women who completed STAI, 14 items were entered into risk ratio regression analysis to assess the characteristics of backgrounds of Kampo users (Table 5). Univariate and multivariate risk ratios are shown in this table. Using univariate analysis, significant predictors of Kampo use were 'Chemotherapy' and 'Uncomfortable side effects of cancer treatment.' Multiple risk ratio regression analysis was performed using stepwise methods. In the multiple risk ratio regression analysis, 'Chemotherapy,' 'State anxiety,' and 'Trait anxiety' were related to use or nonuse of Kampo medicine.

Discussion

This is the first report about the perceptions and attitudes of cancer patients to Kampo medicines. In general, cancer patients tend to seek CAM to relieve the anxiety of recurrence or metastasis and the uncomfortable symptoms accompanying cancer treatment. As shown in Table 1, 46.9% of women had taken Kampo or dietary supplements. These orally administered materials are the top two CAM modalities in Japan [6]. People tend to think that these materials are less toxic for their body than conventional medicine, but several adverse events such as drug hepatitis and interstitial pneumonia have been reported [9]. Among them, only 24.4% of women reported that they talk about their ingestion of Kampo medicine or dietary supplements with their cancer physicians (data not shown). This rate is in accordance with previous research findings in the United States [1]. It is necessary to be aware of the possibility of adverse events induced by CAM modalities when abnormality of liver or kidney function is detected in cancer patients.

In Japan, some Kampo drugs (formulae) are covered by national health insurance. These drugs are authorized by the Japanese government, and their quality is regulated similarly to that of Western-style medicines [6]. Therefore, Japanese physicians and patients tend to regard Kampo medicine as traditional medicine rather than CAM. In this situation, Kampo medicine is considered to be supported by a long history of use, which is lacking for dietary supplements. This background may explain the favorable comments about Kampo medicine in this study.

Because Kampo formulas in Japan are of high quality and contain standardized ingredients, their pharmacologic actions can be studied at the molecular level. Among them, Daikenchuto (DKT) and Rikkunshi-to (RKT) are the best evaluated formulas in terms of their physiological and clinical effects [10]. Most Japanese doctors use these Kampo formulas without paying much attention to the traditional Chinese medicine interpretation of the disease [11]. Because we recruited patients at a gynecology follow-up clinic, not at a Kampo clinic, our data reflect the general status of Kampo medicine in Japan.

This study proved that Kampo users were more likely to have had chemotherapy. Chemotherapy is usually given to advanced, metastatic, or inoperable cancers and is

associated with toxic side effects such as nausea, vomiting, diarrhea, and neuropathy [12]. These characteristics of chemotherapy patients would be the primary reasons for the preference of Kampo use. Moreover, several reports showed the effectiveness of Kampo medicine for the control of these toxic side effects [13, 14]. Japanese doctors would be influenced by these reports and prefer to prescribe Kampo medicine for chemotherapy patients.

This study showed that higher trait anxiety and lower state anxiety were independently associated with Kampo use. Trait anxiety shows the congenital degree of anxiety, so it is quite reasonable that higher trait anxiety was associated with Kampo use. On the other hand, state anxiety shows the present degree of anxiety. It may be that Kampo medication decreased the state anxiety of cancer patients. To clarify such an effect of Kampo medicine, it is necessary to prospectively evaluate the state anxiety before and after Kampo medication.

The limitation of this study is the reliance on self-reported data regarding Kampo or dietary supplement use. The definition of Kampo medicine is somewhat confused with dietary supplements in Japan. To avoid this confusion, we added some explanation about Kampo medicine to the top of the questionnaires. Another limitation of the study is a relatively low response rate of STAI. Among the 420 women who completed parts 1 and 2 of the questionnaire, 321 women completed STAI. STAI consists of two separate sets of 20-item self-rated 4-point scales. Although STAI is a very useful instrument, the fast-paced outpatient setting may preclude study participants from completing two sets of a 20-item scale. To avoid this issue, two types of shorter 6-item version of STAI were developed [15, 16]. It may be convenient to use a shorter version of STAI, but we cannot use it in Japanese. Although we have confirmed that there were no differences in demographic and clinical characteristics between the 420 women who completed parts 1 and 2 of the questionnaire (see Table 1) and the 321 women who completed STAI (see Table 4), we cannot completely refute the possibility of selection bias.

In conclusion, slightly less than one-fourth of Japanese gynecologic cancer patients used Kampo medicine. Kampo users made more favorable comments about Kampo medicine than nonusers. Our findings suggest that the psychological characteristics of individual patients is one factor that can influence the usage of Kampo.

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Conflict of interest No author has any conflict of interest.

References

1. Eisenberg DM, Davis RB, Ettner SL et al (1998) Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. JAMA 280:1569–1575
2. Ernst E, Cassileth BR (1998) The prevalence of complementary/alternative medicine in cancer: a systematic review. Cancer (Phila) 83:777–782
3. Cassileth BR (1999) Complementary and alternative cancer medicine. J Clin Oncol 17:44–52
4. Hyodo I, Amano N, Eguchi K et al (2005) Nationwide survey on complementary and alternative medicine in cancer patients in Japan. J Clin Oncol 23:2645–2654
5. Imanishi J, Watanabe S, Satoh M et al (1999) Japanese doctors' attitudes to complementary medicine. Lancet 354:1735–1736
6. Suzuki N (2004) Complementary and alternative medicine: a Japanese perspective. Evid Based Complement Altern Med 1:113–118
7. Spielberger CD (1983) Manual of the State-Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto
8. Nakazato K, Shimonaka Y (1989) The Japanese State-Trait Anxiety Inventory: age and sex differences. Percept Mot Skills 69:611–617
9. Ishizaki T, Sasaki F, Ameshima S et al (1996) Pneumonitis during interferon and/or herbal drug therapy in patients with chronic active hepatitis. Eur Respir J 9:2691–2696
10. Suzuki H, Inadomi JM, Hibi T (2009) Japanese herbal medicine in functional gastrointestinal disorders. Neurogastroenterol Motil 21:688–696
11. Yu F, Takahashi T, Moriya J et al (2006) Traditional Chinese medicine and Kampo: a review from the distant past for the future. J Int Med Res 34:231–239
12. Sharma R, Tobin P, Clarke SJ (2005) Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea. Lancet Oncol 6:93–102
13. Mori K, Kondo T, Kamiyama Y et al (2003) Preventive effect of Kampo medicine (Hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 51:403–406
14. Nishioka M, Shimada M, Kurita N et al (2011) The Kampo medicine, Goshajinkigan, prevents neuropathy in patients treated by FOLFOX regimen. Int J Clin Oncol. doi:10.1007/s10147-010-0183-1
15. Marteau TM, Bekker H (1992) The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol 31:301–306
16. Chlan L, Savik K, Weinert C (2003) Development of a shortened state anxiety scale from the Spielberger State-Trait Anxiety Inventory (STAI) for patients receiving mechanical ventilatory support. J Nurs Meas 11:283–293

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研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

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Ikeno S, Nagano M, Tanaka S, Nishimura C, Kawamata T, Kawamata M	Gastric tube insertion under visual control with the use of the Pentax-AWS®	J Anesth	25	475-476	2011
川股知之，山本克己，布施谷仁志，平林高暢，坂本明之，川真田樹人	癌性疼痛の発生機序	麻酔	60	1010-1017	2011
川股知之	がん疼痛を科学する	麻酔	60	S177-S182	
川股知之	がん疼痛モデル	ペインクリニック	32	1659-1668	2011