がなされたときには分かっていなかったメカニズムも解明され、はっきりと作用の違う薬物であることが示されたのですから、別法で取り扱うのが妥当だと思われます。また医療用麻薬が乱用されたことがないということは非常にすばらしいことです。さらに運用についても入院中の患者が医療用麻薬をベッドサイドで自己管理することが可能となったり、薬局が医療用麻薬のデッドストックを抱えなくて良いように麻薬小売業者間譲渡を可能にするなど柔軟な対応もなされています。しかしその一方でこれらの規制緩和が十分に周知されていない、または書類手続きの煩雑さから十分に運用されていないことも事実です。緩和医療学会など緩和ケア関連の学会を中心に現場の意見を集約し、行政と話し合いを行っていくことが重要と思われます。今後在宅緩和ケアが浸透してくれば、在宅での余剰麻薬の廃棄に関する取り扱いを適正に行うためのシステム作りも必要になってくると思われます。在宅の主役は医師会が担っています。医師会が中心となって地域の薬剤師などの他職種と定期的な話し合いを行って医療用麻薬適正使用のための意見集約を行うことが重要と思われます。

課題はいろいろありますが、日本の痛み治療は確実に進歩しています。医療と行政が顔の見える関係を構築し、協働して安全で適正な医療用麻薬使用が今まで以上に推進されることを願っています。

1）厚生労働省医薬食品局監視指導・麻薬対策課編集。麻薬・覚せい剤行政の概況（2010年12月）。
2）日本緩和医療学会編。がん疼痛の薬物療法に関するガイドライン2010年版。金原出版株式会社、東京、2010年、pp 55-57。
3）世界保健機関編（武田文和訳）：「がんの痛みからの解放」金原出版、東京、1996。
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5）Suzuki T, Kishimoto Y, Misawa M. Formalin-and carrageenan-induced inflammation attenuates place preferencesproduced by morphine, metamphetamine and cocaine. Life Sci 1996; 59: 1667-74.

東北地方太平洋沖地震災害への
日本医師会が取扱う「義援金」のお願い

— 会員各位のご協力をお願いいたします —

日本医師会では、3月11日に発生した東北地方太平洋沖地震災害の救援、被災地都道府県医師会の支援等のため、全国の医師会員各位からの義援金をお願いしております。

つきましては、長崎県医師会で取り纏めをいたしますので趣旨を御理解下さり、多くの会員各位の御協力をお願い申し上げます。

会員各位の御所属郡市医師会か、次の長崎県医師会口座へ御送金下さいますようお願いいたします。

◎ 長崎県医師会の義援金受付口座
銀 行 名：長崎県医師信用組合　本店
口座番号：普通預金　No. 9 8 0 3 8 4 1
口 座 名：長崎県医師会　東北地方太平洋沖地震　対策本部長
蒔本　恭（マキモト　ヤスシ）

論説と話題

長崎市医師会主催緩和ケア研修会(PEACE)について

長崎市立市民病院緩和ケアチーム　冨安志郎

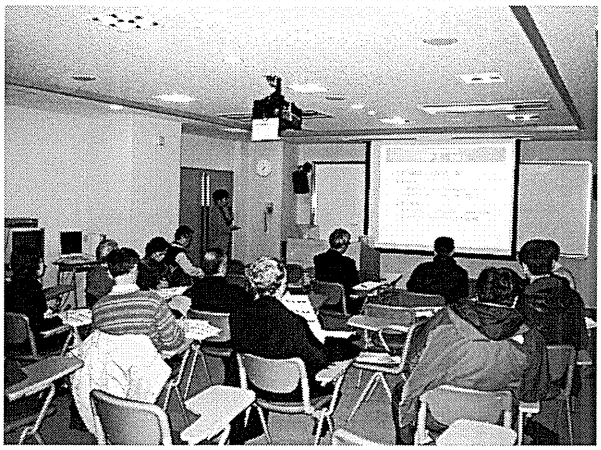
1．PEACE研修会とは

平成19年に策定された「がん対策推進基本計画」には、重点的に取り組むべき課題として化学・放射線治療の推進と専門医師の育成、がん登録の推進と並んで「治療の初期段階からの緩和ケアの実施」があげられています。基本方針として「全国どこでも緩和ケアをがん診療の早期から適切に提供していくためには、がん診療に携わるすべての医師が緩和ケアの重要性を認識し、その知識や技術を習得する必要があることから、緩和ケアに関する大学の卒前教育の充実に努めるとともに、医師を対象とした普及啓発を行い、緩和ケアの研修を推進していく」ことがあげられ、個別目標として「5年以内に、すべてのがん診療に携わる医師が研修等により、緩和ケアについて基本的な知識を習得することとする」ことが決定されました。この目標を達成するために平成20年度～24年度の5年間、全国で医師に対して開催されることになったのが、「がん診療に携わる医師に対する緩和ケア研修会（通称PEACE研修会)」です。

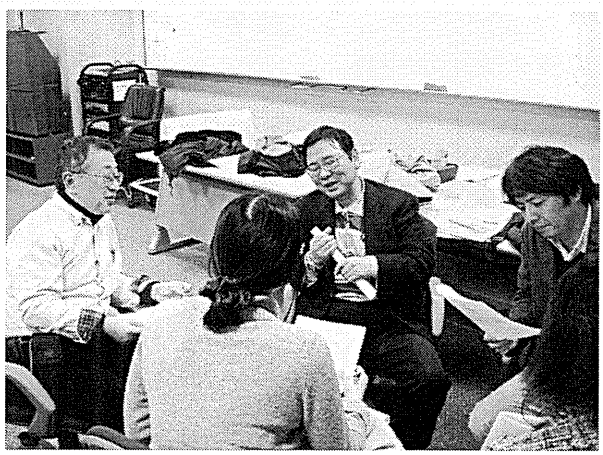
2．長崎市医師会とPEACE研修会

PEACEはPalliative care Emphasis program on symptom management and Assessment for Continuous Educationの大文字の部分をとったちょっと強引なネーミングですが、親しみやすさを売りにしています。がん対策推進基本計画に基づき、厚生労働省と日本緩和医療学会が協働して開催形式とプログラムを作成しました。各都道府県やがん診療連携拠点病院、あるいは医師会が主体となって参加者を募集し、開催形式に則ってプログラムを遂行した場合に、参加者に国から修了証が発行されるシステムになっています。

ちなみに長崎市医師会は戦略研究「緩和ケア推進のための地域プロジェクト（OPTIM)」事業の一環としてこのPEACE研修会を平成20年度より開始しました。プログラムは表1．のような内容となっており、開業されている先生方が受講しやすい木曜日夜間及び土曜日午後に行っております。修了には6コマの講習を受講する必要がありますが、一方向性の「聞くだけ」の講習はなく、インタラクティヴな形式の講義やグループワーク、ロールプレイを取り入れ、全員参加型で退屈しないように工夫されています。痛みに対する医療用麻薬の使い方、痛み以外でがん患者にしばしば見られる呼吸困難や消化器症状のマネジメントといった身体症状についての講習や、不安、抑うつ、せん妄といったがん患者によくみられる精神症状の見つけ方や対処の方法、がん告知、再発といったバッドニュースを伝えるコミュニケーションスキル、在



講　義



コミュニケーションロールプレイ

地域連携グループワーク

宅緩和ケアへの移行のための地域連携、など幅広く学ぶことができます(写真、受講風景)。

このプログラムは長崎県内のがん診療連携拠点病院が行っているPEACE研修会と同じ内容となっております。もし長崎市医師会のPEACE研修会で6コマ全てを受講できなくても、欠けたコマのみを各がん診療連携拠点病院で行われている研修会で受講すれば修了できるようになっております。長崎市医師会は今後もがん診療連携拠点病院と連携を取りながらPEACE研修会を継続していく予定です。

3．受講のメリット

本プロジェクトや県医師会、がん診療連携拠点病院等で開催しておりますPEACEの所定の単位を修了された医師が、がん患者に対してWHO方式がん性疼痛治療法に基づき、がん性疼痛の症状緩和を目的として計画的な治療管理及び療養上必要な指導を行って麻薬を処方した場合、月1回100点の算定が可能となります（B001－22　がん性疼痛緩和指導管理料)。

- 九州厚生局（長崎事務所）への届け出が必要です。
- インターネットで下記URLより九州厚生局のホームページにアクセスして下さい。
  http://kouseikyoku.mhlw.go.jp/kyushu/
- 「申請、届出等の手続き案内」→「施設基準の届出等」→「特掲診療料の届け出一覧」→「特掲診療料の施設基準等及びその届け出に関する手続きの取り扱いについて（平成22年3月5日)」と進み、別添2（正副2部）および様式5の2を作成し、緩和ケア研修会修了書の写しとともに下記に届け出を行ってください。

  九州厚生局長崎事務所
  〒850-0033　長崎市万才町7－1　住友生命ビル12F
  電話：095—801—4201

これまでに120名以上の先生方が受講され、平成20～22年度の３年間で70名の先生方が６コマすべてを修了されました。ちなみに、平成22年12月時点での長崎県全体の修了者数が348名ですから、約２割の方が何らかの形で当研修会を経て、修了されたことになります。がん患者数に対する修了者数の割合は都道府県別にみて長崎県は全国７位（修了者１人あたりのがん患者数43名）という高水準にあり、当医師会研修会が長崎県の緩和ケアレベル向上に寄与していることがうかがえます。修了がお済みでない先生方には今後とも随時開催のご案内を差し上げますので、最後まで受講いただきますようお願い申し上げます。

４．受講に際しまして

医療の進歩は、亡くならないけど治らない、治らないけど病院に入院している必要のない病態を作り出しました。こうした病態は昭和の頃にはあまりなかったもので、疾病構造が変化してきているといえます。がんもその一つだと思います。治らないけどがんと共存し、QOL を維持して希望の療養生活を送ることは十分可能であり、緩和ケアはそれを支えるスキルだと思います。多くの先生方が緩和ケアとは患者さん、家族のつらさを支える医療であること、多職種と連携すること、病院・在宅・ホスピスの連携を促進すること、などをイメージしながら受講していただくことを願っています。

表１

平成22年度　長崎市医師会緩和ケア研修会

① 地域連携と治療・療養の場の選択（１単位）……「Ⅰ．緩和ケア基礎」
開催日　平成22年12月２日(木)　　時　間　19：00～21：00（120分）

② がん性疼痛ワークショップ（２単位）……「Ⅴ．疼痛緩和ＷＳ」
開催日　平成23年１月８日(土)　　時　間　15：00～18：50（230分）

③ コミュニケーション技術（２単位）……「Ⅵ．コミュニケーションWS」
開催日　平成23年１月16日(日)　　時　間　13：00～16：50（230分）

④ がん性疼痛の評価と治療（１単位）……「Ⅱ．がん性疼痛緩和」
開催日　平成23年１月20日(木)　　時　間　19：00～20：50（110分）

⑤ 痛み以外の身体症状（１単位）……「Ⅲ．疼痛以外の身体的ケア」
開催日　平成23年２月３日(木)　　時　間　19：00～20：50（110分）

⑥ 気持ちのつらさとせん妄に対するケア（１単位）…「Ⅳ．精神的ケア」
開催日　平成23年２月17日(木)　　時　間　19：00～20：50（110分）

ANTICANCER RESEARCH *31*: 1483-1488 (2011)

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

S. IWASE[1], D. YAMAMOTO[2], Y. KURODA[1], T. KAWAGUCHI[3], K. KITAMURA[4], H. ODAGIRI[5], S. TERAMOTO[4], K. AKAZAWA[6] and Y. NAGUMO[7]

[1]*Department of Palliative Medicine, University of Tokyo Hospital, Tokyo, Japan;*
[2]*Department of Surgery, Kansai Medical University, Hirakata, Osaka, Japan;*
[3]*Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan;*
[4]*Department of Breast Surgery, Kyushu Central Hospital, Fukuoka, Japan;*
[5]*Department of Surgery, Hirosaki University School of Medicine, Hirosaki, Japan;*
[6]*Department of Medical Informatics, Niigata University Medical Hospital, Niigata, Japan;*
[7]*Breast Unit, Nagumo Clinic, Tokyo, Japan*

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.*

Correspondence to: Daigo Yamamoto, MD, Department of Surgery, Kansai Medical University, Hirakata, Osaka 570-8507, Japan. Tel: +81 728040101, Fax: +81 728040170, e-mail: yamamotd@hirakata.ac.jp

Key Words: Sequential therapy, adjuvant chemotherapy, breast cancer.

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

0250-7005/2011 $2.00+.40

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

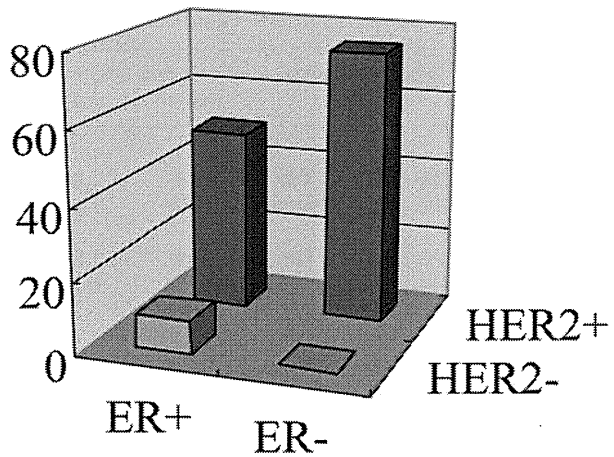


Figure 1. *Relationship between pCR and HER2/ER status.*

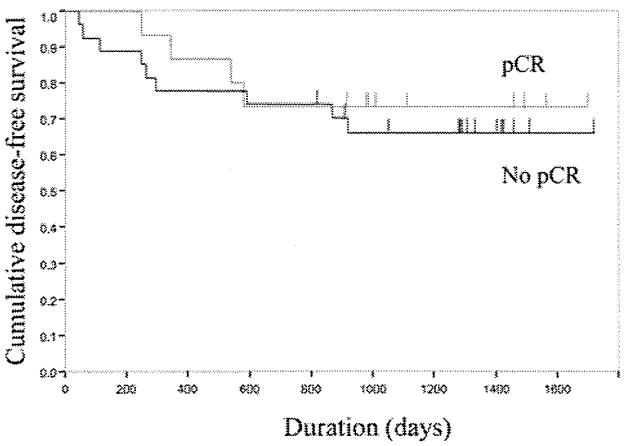


Figure 2. *Relationship of pCR and non-pCR to disease-free survival.*

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.

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

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%)

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.

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

Makiko N Mieno[1*], Takuhiro Yamaguchi[2] and Yasuo Ohashi[3]

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.

* Correspondence: mnaka@jichi.ac.jp
[1]Department of Medical Informatics, Center for Information, Jichi Medical University, Shimotsuke, Japan
Full list of author information is available at the end of the article

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

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

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

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

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

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

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

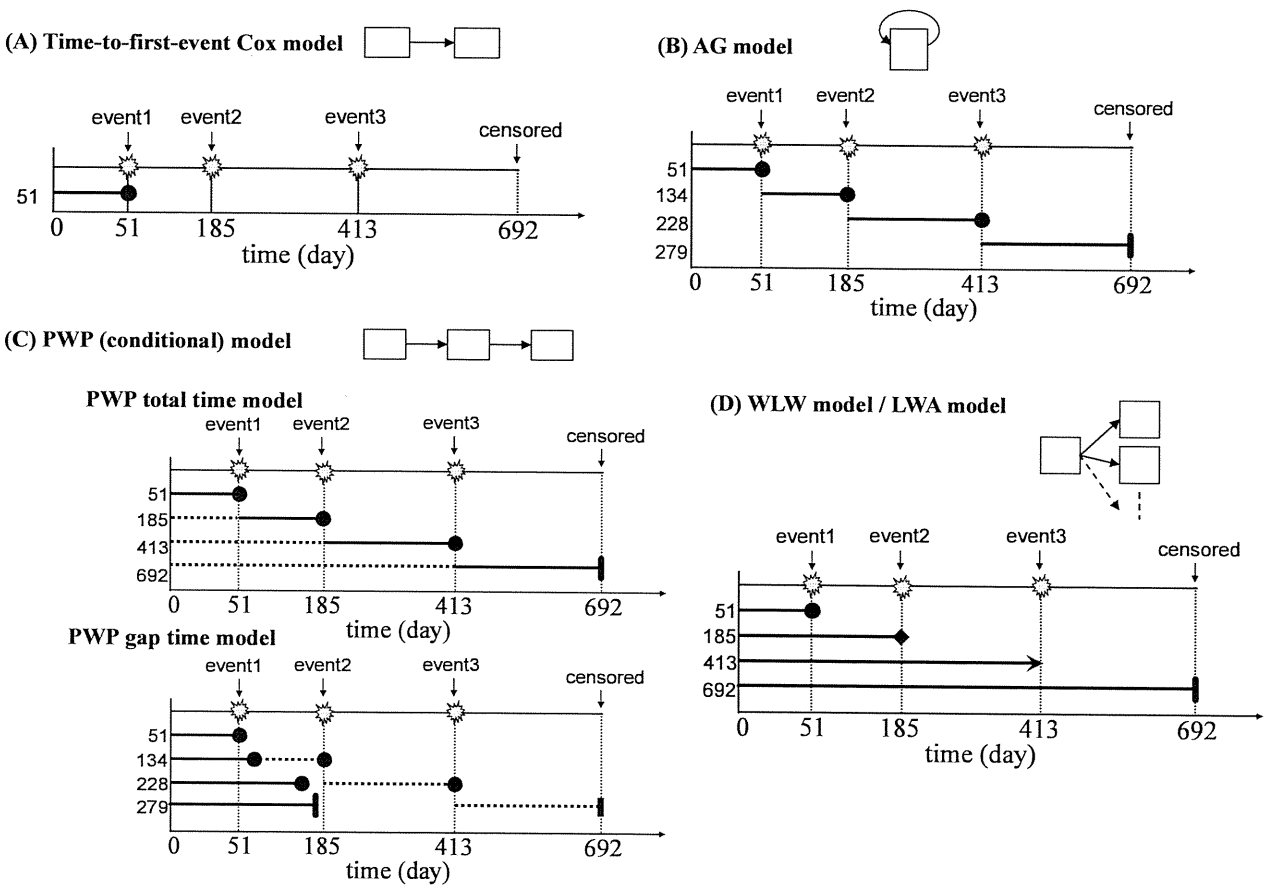

Figure 1 Schematic forms of the various extended time-to-event Cox regression models. Each arrow represents a stratum. Arrow diagrams describe about the behavior of ID = 1 in the sample data (DATA = MS) in Appendix (Additional file 1), who experiences the first event at day 51, second event at day 185, 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

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

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

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

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

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

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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Author details

[1]Department of Medical Informatics, Center for Information, Jichi Medical University, Shimotsuke, Japan. [2]Department of Biostatistics, Tohoku University School of Medicine, Sendai, Japan. [3]Department of Biostatistics, School of Public Health, University of Tokyo, Bunkyo, Tokyo, Japan.

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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ORIGINAL ARTICLE

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

Takashi Takeda · Takuhiro Yamaguchi · Nobuo Yaegashi

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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

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 prescibe them conveniently, just like a Western-style powder. In this situation, Kampo medicine is the CAM that is most frequently used

T. Takeda (✉)
Department of Traditional Asian Medicine,
Tohoku University Graduate School of Medicine,
1-1 Seiryo-machi, Aoba, Sendai 980-8574, Japan
e-mail: take@med.tohoku.ac.jp

T. Yamaguchi
Division of Biostatistics,
Tohoku University Graduate School of Medicine,
1-1 Seiryo-machi, Aoba, Sendai 980-8574, Japan

N. Yaegashi
Department of Obstetrics and Gynecology,
Tohoku University Graduate School of Medicine,
1-1 Seiryo-machi, Aoba, Sendai 980-8574, Japan

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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.