【表3】盲検の有無に基づくランダム化比較試験の分類

	臨床試験の間、参加者が受ける治療について知っている人	
	医師	患者
非盲検試験（オープン試験） 治療に関わる全ての人が、どんな治療が行われているかを知っている	○	○
単盲検試験（シングルブラインド） 医師だけが、患者さんがどんな治療を受けているかを知っている	○	×
二重盲検試験（ダブルブラインド） 医師と患者さん両方とも、どんな治療が行われているか知らない	×	×

臨床試験の相と病期分類のステージの違い －膵臓がんの例－

なお、がん治療の臨床試験に初めて参加された方の中には、「臨床試験の相」と「がんの病期（ステージ）」とを混同される方がいらっしゃいます。ステージは、がんの大きさやリンパ節移転、他の臓器への転移などによって規定される、がんが体内でどれくらい広がっているかを表す指標です。膵臓がんのステージには、国際的に使用されている国際対がん協会（UICC）のTNM分類（図1参照）と、日本で使用されている日本膵臓学会（JPS）（図2参照）による分類がありますので、担当の先生からステージについてお聞きになる場合はどちらの分類に基づいたものなのかを確認されると良いでしょう。

【図1】膵臓がんのステージ分類（UICC分類）

	M0		M1
	N0	N1	Nに関係なく
Tis	0		
T1	IA	ⅡB	Ⅳ
T2	IB		
T3	ⅡA		
T4	Ⅲ		

分類	
Tis	非浸潤がん
T1	膵内に限局≦2cm
T2	膵内に限局＞2cm
T3	膵外に進展
T4	腹腔動脈幹または上腸間膜動脈に浸潤

分類	
N0	所属リンパ節転移なし
N1	所属リンパ節転移あり
M0	遠隔転移なし
M1	遠隔転移あり

UICC：悪性腫瘍の分類［第7版］より改変

【図2】膵臓がんのステージ分類（ＪＰＳ分類）

	M0			M1	
	N0	N1	N2	N3	
Tis	0				
T1	Ⅰ	Ⅱ	Ⅲ	Ⅳb	
T2	Ⅱ	Ⅲ	Ⅲ		
T3	Ⅲ	Ⅲ	Ⅳa		
T4	Ⅳa				

分類	
Tis	非浸潤がん
T1	膵内に限局≦2cm
T2	膵内に限局＞2cm
T3	膵内胆管、十二指腸、膵周囲組織に浸潤
T4	隣接する大血管、膵外神経叢、他臓器に浸潤

分類	
N0	膵関連リンパ節転移なし
N1～3	膵関連リンパ節転移あり（数字はリンパ節群を表す）
M0	遠隔転移なし
M1	遠隔転移あり

日本膵臓学会編：膵癌取扱い規約［第6版］より改変

新しい薬が承認され市販されるまでの流れ

以下の図は、新薬が承認されるまでの流れを示したものです。

【図3】新薬が承認されるまでの流れ

非盲検試験	開発段階		適応省令
創製化合物数＝約30万	基礎研究 2～3年	新規物質の探索・創薬	
		物理化学的研究	
	非臨床試験 3～5年	薬効薬理試験	ＧＬＰ
		一般薬理試験	
		一般毒性・特殊毒性研究	
		薬物動態研究	
	臨床試験（治験） 3～7年	第Ⅰ相試験（臨床薬理試験）	ＧＣＰ
		第Ⅱ相試験（探索的試験）	
		第Ⅲ相試験（検証的試験）	
	承認審査 1～2年	承認申請	
		承認審査	
承認取得数＝50		医薬品製造（輸入）承認・許可	

ICR臨床研究入門のウェブサイト（ICRweb）より引用　http://www.icrweb.jp/

最初に新しい物質（シーズ）の検索や、薬の形にする創薬、物理化学的な性質を調べる基礎研究があり、その後、安全性や効果を細胞や動物に対して検討する非臨床試験が実施されます。これらの過程を経て、ようやく人に対する臨床試験（治験）というステップに進み、数年かけて安全性と効果が調査されます。

治験にて良い結果が出た薬は、いよいよ医薬品としての承認取得へと進みます。日本では、承認のための審査実務は「独立行政法人医薬品医療機器総合機構」※7（以下「PMDA」）という組織が行っています。承認のプロセスは、まず治験の主体者が承認申請者としてPMDAに厚生労働大臣宛の申請書を提出します。提出された書類をPMDAで審査し、その上で厚生労働省の中にある薬事・食品衛生審議会の諮問・答申を経て、厚生労働大臣より薬事法に基づく承認が得られるということになります。薬事法による承認後は、原則として60日以内、遅くとも90日以内に薬価（薬の公定価格）が決まり、医療保険の中で使用できるようになります。

以上のように、一つの薬を育てて診療の中で生かしていくというプロセスは、膨大な費用と手間、時間がかかることがおわかりいただけると思います。

用語のヒント

※7 独立行政法人医薬品医療機器総合機構（PMDA）

厚生労働省所管の独立行政法人であり、英語名称（Pharmaceuticals and Medical Devices Agency）の頭文字をとりPMDAとも呼ばれます。医薬品の副作用などによる健康被害救済業務、薬事法に基づく医薬品・医療機器などの審査関連業務、医薬品や医療機器などの品質を確保する安全対策業務を行っており、日本版FDA※8ともいわれています。しかしながら、FDAに比べてPMDAの職員数は圧倒的に少なく、小規模です。

※8 FDA（Food and Drug Administration）

米国の食品医薬品局のことです。米国食品医薬品局は、日本の厚生労働省にあたる米国の保健社会福祉省（DHHS：Department of Health and Human Services）に属している政府の一機関です。米国内の「食品・医薬品・健康食品・化粧品」等についての厳しい品質検査、および承認審査を行い、消費者保護の権限を与えられています。

臨床試験の情報に関して

2005年度より、臨床試験は「臨床試験データベース」に登録されることが推奨されています。日本国内で行われている臨床試験のデータベースには、大学病院医療情報ネットワーク研究センター（通称：UMINセンター）、財団法人 日本医薬情報センター（JAPIC）、社団法人日本医師会 治験促進センターなどがあります。これらの情報に関しては、担当医の先生とご相談されたり、セカンドオピニオンを受けたりされると良いでしょう。また、インターネットサービス（独立行政法人国立がん研究センターがん対策情報センターがん情報サービスのウェブサイトの「がんの臨床試験一覧」（http://ganjoho.jp/professional/med_info/clinical_trial/index.html）などを利用されるのも良いと思います。参加できる臨床試験があるかどうかは、膵臓がんのステージや膵臓がんに関する治療歴、全身状態などにより異なりますので、担当の先生によくご確認ください。

（上記に紹介しているサイトは、本書P86～P87をご参照ください。）

代替療法などに関して

がんの治療では通常、手術、放射線治療、化学療法（抗がん剤）が中心的な役割を果たしており、膵臓がんも例外ではありません。しかし、それらの治療には限界があることも事実であり、特に膵臓がんのように有用性が示されている抗がん剤が少ない疾患に関しては、多くの患者さんやご家族が上記以外の治療方法、例えば免疫療法や温熱療法、漢方、健康食品、サプリメントなどを考えられるのではないかと思います。

これらの療法の多くは、これまで述べてきたような臨床試験が過去に実施・報告されていないことから、科学的根拠に基づいて推奨することは難しいレベルにあります。しかし、最近ではこれらの療法においても有効性や安全性を科学的な方法で評価しようという気運が世界的に高まっており、一部の免疫療法などでは膵臓がんに関しても臨床試験が実施され始めています。全ての代替療法に臨床試験という手法がなじむわけではないと思いますが、臨床試験には「将来同じような病気になる患者さんへの財産（次世代への贈り物）」という側面があります。新しい治療が有用であることを証明するためには、大変な労力と時間、費用がかかることがこの章をお読みいただいた方にはおわかりいただけると思いますが、有望と思われる治療に関しては将来像を見据えた開発を行うことが研究にたずさわる者の責務と考えます。

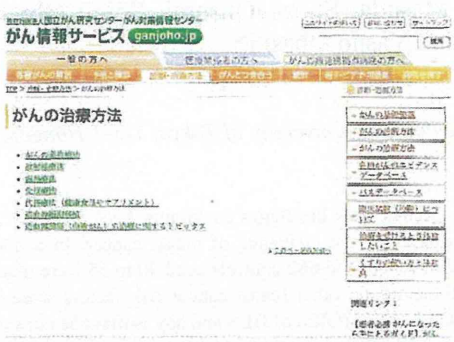
代替療法に関しては、独立行政法人国立がん研究センターがん対策情報センターがん情報サービスのウェブサイトの「がんの治療方法」（http://ganjoho.jp/public/dia_tre/treatment/index.html）や独立行政法人国立健康・栄養研究所のウェブサイトの「素材情報データベース」（http://hfnet.nih.go.jp/contents/indiv.html）、独立行政法人病院機構四国がんセンターのウェブサイトの「がんの代替医療の科学的検証に関する研究」（http://www.shikoku-cc.go.jp/kranke/cam/index.html）などもご参照ください。（上記のウェブサイトは、次ページで紹介しています）

〈参考文献〉
本章の作成にあたり、アメリカのNPO法人 PanCAN（Pancreatic Cancer Action Network）の医療ブックレット「Clinical Trial」のほかに、以下の文献・資料を参考にしました。
（1）ICR臨床研究入門のウェブサイト（ICRweb）http://www.icrweb.jp/
（2）独立行政法人国立がん研究センターがん対策情報センター
がん情報サービスのウェブサイト　http://ganjoho.jp/public/index.html

代替療法について解説されているサイト

国立がん研究センター がん情報サービス「がんの治療方法」

http://ganjoho.jp/public/dia_tre/treatment/index.html



「がん情報サービス」内の「がんの治療方法」のページで、様々ながんの治療法とともに「代替療法（健康食品やサプリメント）」が紹介されています。

国立健康・栄養研究所「素材情報データベース」

https://hfnet.nih.go.jp/contents/indiv.html

国立健康・栄養研究所の「『健康食品』の安全性・有効性情報」のページの右下に「素材情報データベース」のコーナーが設けられており、素材の名前で検索ができます。

四国がんセンター「がん代替医療の科学的検証に関する研究」

http://www.shikoku-cc.go.jp/kranke/cam/index.html

左のサイトでは「がんの補完代替医療ガイドブック【第３版】（2012年）」が公開されており、自由にダウンロードができます。

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Probiotic Beverage with Soy Isoflavone Consumption for Breast Cancer Prevention: A Case-control Study

Masakazu Toi, Saya Hirota, Ai Tomotaki, Nobuaki Sato, Yasuo Hozumi, Keisei Anan, Takeshi Nagashima, Yutaka Tokuda, Norikazu Masuda, Shozo Ohsumi, Shinji Ohno, Masato Takahashi, Hironori Hayashi, Seiichiro Yamamoto and Yasuo Ohashi*

Department of Biostatistics, School of Public Health, The University of Tokyo, 7-3-1 Hongou, Bunkyo-ku, Tokyo, 113-0033 Japan

Abstract: The purpose of this study is to evaluate how beverages containing *Lactobacillus casei* Shirota (BLS) and soy isoflavone consumption since adolescence affected the incidence of breast cancer. In a population-based case-control study, three hundred and six cases with breast cancer and 662 controls aged 40 to 55 were matched for age and residential area and included in the analyses. Diet, lifestyle and other breast cancer risk factors were investigated using the self-administered questionnaire and interview. Odds ratios (ORs) of BLS and soy isoflavone consumption for breast cancer incidence were independently and jointly estimated using a conditional logistic regression. The ORs of BLS consumption (≥ four times a week against < four times a week) was 0.65 and statistically significant ($p = 0.048$). The analysis of association between soy consumption and breast cancer incidence showed the more the isoflavone consumption is, the lower the odds of breast cancer becomes. Adjusted ORs for breast cancer in the second, the third and the fourth quartiles of soy consumption against the first quartile were 0.76, 0.53 and 0.48, respectively (trend test, $p = 0.0002$). The BLS-isoflavone interaction was not statistically significant; however, a biological interaction was suggested. Regular consumption of BLS and isoflavones since adolescence was inversely associated with the incidence of breast cancer in Japanese women.

Keywords: Breast cancer, *Lactobacillus casei* Shirota, probiotic beverage, soy isoflavones.

1. INTRODUCTION

The breast cancer incidence in Japan had been lower compared to the Western countries; however, rapid increase of the incidence was observed in the past 10 to 15 years as in other Asian countries [1]. The number of new breast cancer cases in Japanese women surpassed that of stomach cancer to become the most frequent of all cancers in 1994. An estimated 45700 women were newly diagnosed with breast cancer in 2003 (an estimated 36500 with stomach cancer) [2]. One of the likely causes of the rapid increase in Japan is the increased estrogen exposure [3], one of the important breast cancer risk factors, which is due to delayed first delivery and decreased number of child births. However, only about 40% of the increase can be explained by age of menarche, age of menopause, age of having the first child, and number of births. Changes in the traditional Japanese lifestyle and increase of obesity are possible contributing factors [4].

Beverages containing *Lactobacillus casei* Shirota (BLS, Yakult®, Yakult Honsha, Co. Ltd., Tokyo, Japan) have been sold in Japan since 1935. According to the manufacturer's data, 84% of BLS were sold through a unique personal home and office delivery system in 1985, and the product took up an estimated 50% or more of the Japanese fermented dairy product market in 1970s and 1980s.

A Japanese case-control study showed regular consumption of BLS was inversely associated with occurrence of bladder cancer [5]. *Lactobacillus casei* Shirota was shown to prevent recurrence of colon polyp in a randomized trial [6] and to prevent recurrence of superficial bladder cancer in two randomized trials [7, 8]. The cancer preventive effect of BLS may be explained by potentiation of natural killer (NK) cell activation by *Lactobacillus casei* Shirota and NK cell-mediated antitumor activity [9].

The association between soy consumption and occurrence of breast cancer has been evaluated in a number of epidemiological studies. Studies in Japan showed that soy consumption was inversely associated with occurrence of breast cancer in a cohort study by Yamamoto and colleagues [10], and Hirose [11] reported the same association in a hospital-based case-control study. A meta-analysis conducted by Wu and colleagues [12] also showed an inverse association when the analysis included only studies conducted in Asian countries where soy consumption is high.

The mechanism of soy to prevent breast cancer may be ascribed to estrogenic and anti-estrogenic actions of isoflavones such as genistein and daidzein contained in soy. In a nested case-control study conducted along with the Japanese cohort study [13], an inverse association between serum isoflavone level and occurrence of breast cancer was reported. Intestinal flora is known to affect the isoflavone me-

*Address correspondence to this author at the Professor, Department of Biostatistics, School of Public Health, The University of Tokyo, 7-3-1 Hongou, Bunkyo-ku, Tokyo, 113-0033 Japan; Tel: +81-3-5841-3518; Fax: +81-3-3814-2779; E-mail: ohashi@epistat.m.u-tokyo.ac.jp

2212-3881/13 $58.00+.00

tabolism, especially the metabolism of an isoflavone phytoestrogen daidzein [14].

On the other hand, consumption of BLS was shown to affect the intestinal flora in a randomized double-blind study [15], suggesting BLS consumption may modify the preventive effect of soy isoflavones against breast cancer.

Based on these findings, we evaluated the role of probiotic beverages in breast cancer prevention in Japanese women with implication of soy isoflavone consumption in a population-based case-control study. The study is to explore the cause of the recent rapid increase of breast cancer in Japan and the possibility of breast cancer prevention by lifestyle modification.

2. MATERIALS AND METHODS

2.1. Study Setting and Participants

This population-based case-control study took place in 14 areas in Japan. The catchment areas were selected so that both rural and urban areas were covered. Cases were defined as Japanese women aged 40 to 55 at the time of consent, who had undergone operation for the International Union against Cancer Tumor Node Metastasis (UICC-TNM) Stage 0 or I unilateral or bilateral primary breast cancer at one of 14 study centers within one year prior to participation. Women who had breast cancer of UICC-TNM Stage II or higher and those with other types of cancer were excluded.

Controls were Japanese women living in the catchment areas aged between 40 and 55 without past or present breast cancer. Women aged 40 to 55 were first picked out from the catchment areas based on the Basic Resident Register, and potential controls were randomly selected. Once a case was included in the study, controls matched to the case for age (the range of target age was divided into two-year brackets) and residential area were randomly selected from the pool of candidate controls and invited to participate. Invitation letters were sent until two controls were selected for a case.

The study was approved by the institutional review board of all study centers. Cases and controls were recruited between October 9, 2007 and March 31, 2009. Informed consent was obtained from all cases and controls enrolled in the study.

2.2. Procedures

A self-administered questionnaire survey and interviews were conducted. To avoid recall biases, participants were asked about their past BLS and soy consumption in interviews. Frequency and duration of BLS consumption and frequency and amount of soy (six items including miso-soup and tofu) consumption during three predetermined time periods; around the age 10 to 12, around the age 20, and 10 to 15 years prior to the study; were asked in the questionnaire. We conducted a self-administered questionnaire survey to ask about their diet (including alcohol consumption), exercise, medical history, and family history during the year before their breast cancer diagnosis to cases and during the year before the survey to controls. We used a self-administered food frequency questionnaire created based on the food frequency questionnaire developed by the Japan National Cancer Center (JNCC) [16], of which validity has been confirmed in the previous study showing the effect of soy consumption in the prevention of breast cancer [10].

Cases and matched controls were interviewed by the same trained interviewer who was blinded to the case/control status. A set of self-administered questionnaire forms was handed to each participant at the time of consent. Completed questionnaire forms were kept by participants until the interview and checked by interviewers for omission.

2.3. Exposure Assessment

BLS and isoflavone consumption in the three predetermined time periods was averaged for the purpose of analysis. BLS consumption was classified into regular consumption ($\geq$ 4 times a week) and no consumption ($<$ 4 times a week). Isoflavone consumption was calculated based on the frequency and the amount of the six food items and classified into quartiles according to the daily consumption in the control group: $>$ 43.75 mg/day (the fourth quartile), 28.81 to 43.75 mg/day (the third quartile), 18.76 to 28.81 mg/day (the second quartile), and $<$ 18.76 mg/day (the first quartile).

2.4. Statistical Analysis

Based on a hypothesized OR of 0.55 and a 15% prevalence of exposure to BLS in the control group, the target sample size was calculated to be 355 for cases and 710 for controls to achieve a 80% power with a 5% two-sided type I error. We calculated ORs and 95% confidence intervals (CIs) using a conditional logistic regression model. P-values for potential dose-response of soy isoflavone consumption on breast cancer were calculated based on the same regression model using linear scores. We also performed a subgroup analysis of association between BLS consumption and breast cancer occurrence according to menopausal status.

Cases and controls were matched for age and area of residence for one analysis and for area of residence alone for a separate analysis. Robustness of the results was also examined in a sensitivity analysis using an unconditional logistic regression model, which adjusted the matching variables as covariates. All p-values were two-sided.

Education, physical activity level, history of benign mammary tumor, family history of breast cancer, past/current use of female sex hormones before menopause, age at menarche, number of childbirth, breastfeeding experience, birth weight, BMI at the age 20, smoking status, and current energy intake were taken into account as potential confounders.

We used the SAS LOGISTIC procedure (version 9.1; SAS Institute, Cary, NC) for all analyses.

2.5. Role of the Funding Source

The sponsor organized the study group under one of the projects of Comprehensive Support Project for Oncology Research (CSPOR) [17, 18]. The independent ethics committee and the epidemiology committee of CSPOR approved the study protocol. The funding source of the study, Yakult Honsha Co. Ltd., was not involved in the study design, data collection, data analysis, data interpretation or writing of the

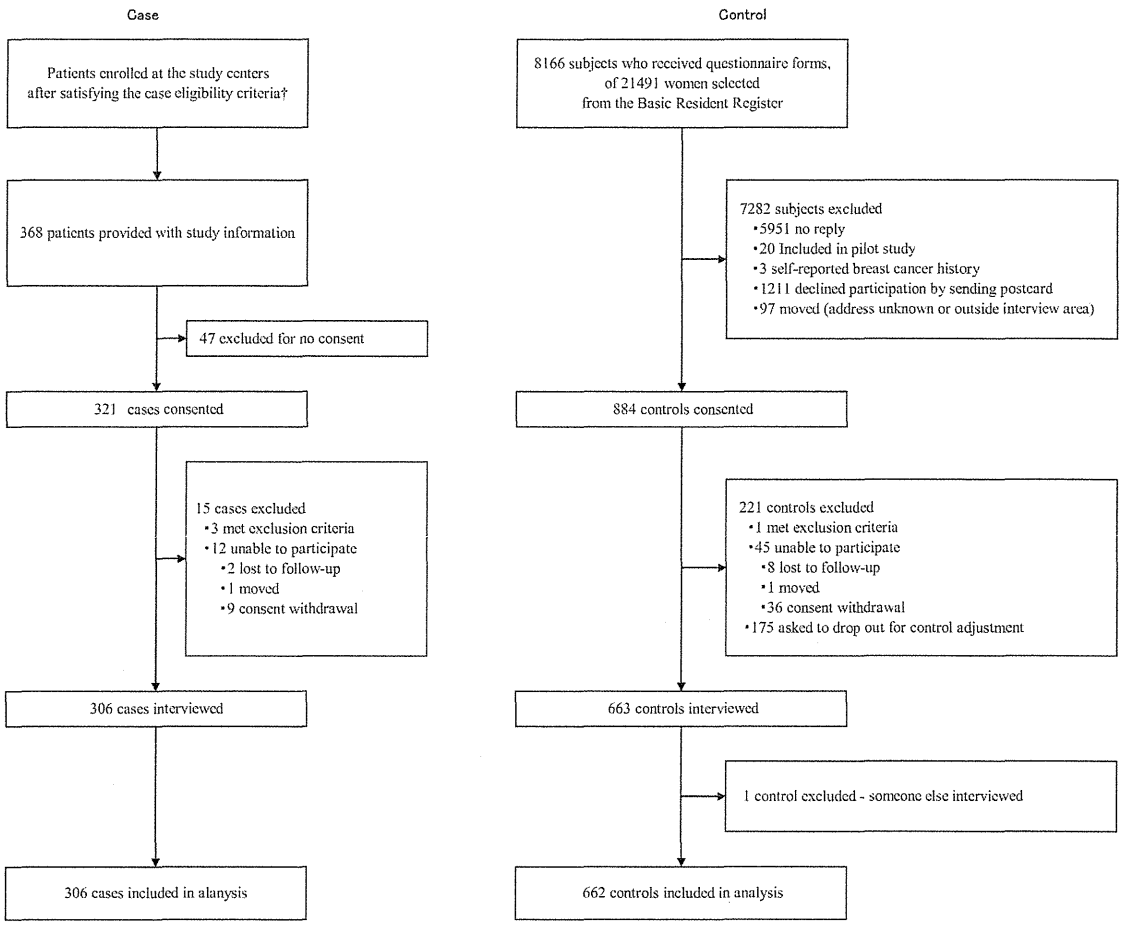

Fig. (1). Study profile.
†: Data for the number patients screened are not available.

study reports. The corresponding author had full access to all the study data and had final responsibility for the decision to submit the study report for publication.

3. RESULTS

(Fig. **1**) presents a flow chart of the case and control recruitment process. One control was excluded because we later found out her mother had filled out the questionnaire forms and had been interviewed. Baseline characteristics of 968 participants, including two cases and 32 controls not matched for age due to some adjustment in the sampling procedure, are shown in (Table **1**). Statuses of estrogen receptor, progesterone receptor and human epidermal growth factor receptor in cases are shown in (Table **2**).

Crude ORs (matched for age and area of residence) and adjusted ORs (matched for area of residence and adjusted for the age and other confounding factors) for breast cancer in women who had consumed BLS $\geq$ four times per week against those who had consumed < four times per week were 0.66 (95% CI, 0.43–1.02; p = 0.061) and 0.65 (95% CI, 0.42–1.00; p = 0.048), respectively. (Table **3**) Crude ORs for isoflavone consumption in the second, the third and the fourth quartiles against the first quartile were 0.74 (95% CI, 0.49–1.10), 0.58 (0.38–0.88) and 0.52 (0.34–0.79), respectively. (Trend test, p = 0.0012) Adjusted ORs were 0.76 (0.52–1.13), 0.53 (0.35–0.81) and 0.48 (0.31–0.73), respectively (trend test, p = 0.0002; Table **3**).

We present the results of adjusted analysis based on a model in which participants were matched for residential area and age and categorized into the age brackets of 40s and 50s. Categorical age was used as an explanatory variable. The number of participants included in the analysis was maximized with this model. The results were mostly comparable to those of a logistic regression analysis in which the matching factors were adjusted as covariates.

Significant breast cancer risk factors used for adjustment included above high school-level education (adjusted ORs, 0.61 for the BLS analysis and 0.63 for the isoflavone analysis), benign tumor (adjusted ORs, 3.0 and 3.2), and family history of breast cancer (adjusted ORs, 2.1 and 2.2).

Table 1. Baseline Characteristicss

	Case (n=306)		Control (n=662)	
Age (years)	48	(4·1)	47	(3·7)
40-49	199	(65·0%)	461	(69·6%)
50-55	107	(35·0%)	201	(30·4%)
Educational background				
Other than college/graduate	264	(86·3%)	518	(78·3%)
College/graduate school or above	42	(13·7%)	144	(21·8%)
Physical activity level (METs/day)	26	(13·3)	27	(12·8)
Benign mammary tumor	51	(16·7%)	41	(6·2%)
Family breast cancer history	29	(9·5%)	28	(4·2%)
Age at menarche (years)	13	(1·3)	13	(1·3)
Number of births	2	(1·0)	2	(1·1)
Breastfeeding experience	232	(75·8%)	528	(79·8%)
Menopause	111	(36·3%)	200	(30·2%)
Use of female sex hormone before menopause				
Not using	254	(83·0%)	553	(83·5%)
Currently using	52	(17·0%)	109	(16·5%)
Birth weight				
≥ 2500g	270	(88·2%)	584	(88·2%)
< 2500g	21	(6·9%)	48	(7·3%)
Unknown/data not available	15	(4·9%)	30	(4·5%)
BMI at the ave. age of 20(kg/m^2)	20	(2·4)	20	(2·2)
Smoking	38	(12·4%)	78	(11·8%)
Energy intake (1000kcal/day)	2.16	(0·8)	2.14	(0·8)

Data are n (%) or mean (SD).

According to an analysis using a multiplicative factor, the interaction between BLS and isoflavones was not statistically significant (p = 0.87) but there was a trend of weaker dose-response relationship between isoflavone consumption and breast cancer as observed from the flat curve in women who consumed more BLS (Fig. **2**).

A subgroup analysis according to menopausal status (matched for area of residence and adjusted for age and other confounding factors) showed an adjusted OR in premenopausal women was 0.78 (95% CI, 0.46–1.32; p = 0.35) and that in postmenopausal women was 0.43 (0.19–0.99, p = 0.046) (Table **4**).

An additional analysis according to time period of BLS consumption (age 10 to 12, around the age 20, and 10 to 15 years prior to the study) showed adjusted ORs of BLS consumption ≥ four times per week to BLS consumption < four times per week were 0.86 (95% CI, 0.60–1.23; p = 0.41), 0.58 (0.37–0.92, p = 0.019) and 0.84 (0.57–1.24, p = 0.38), respectively.

4. DISCUSSION

Strengths of this study include (1) robustness of data, which were mostly comparable across the sensitivity analyses with different adjustments for confounders, (2) identification of known risk factors such as family history of breast cancer and history of benign tumor, (3) being a population-based study enrolling participants from multiple areas in Japan, (4) smaller biases due to an interview survey compared with a self-administered questionnaire survey, and (5) successful interviewer blinding. The interviewers were asked whether they had found out the case/control identity of the interviewees during interviews. They answered they had been able to identify cases and controls in 29% of the interview sessions, and they were incorrect about the case/control identification in 24% of the time. Therefore, the blinding was considered successful. As the limitations of this study recognized the following: While validated questionnaire forms [15] were used for the survey on current food consumption, the survey on past food consumption was not validated.

Table 2. Hormone Receptor Status in Cases

	Case (n=306)	
Estrogen receptor		
Negative	28	(9.2%)
Positive	259	(84.9%)
Unknown	19	(6.2%)
Progesterone receptor		
Negative	60	(19.6%)
Positive	227	(74.2%)
Unknown	19	(6.2%)
HER2 receptor		
Negative	222	(72.6%)
Positive	36	(11.8%)
Unknown	48	(15.7%)

Data are n (%).

However, the BLS distributor's sales record and BLS consumption estimated based on the completed questionnaire forms were cross-checked and proven highly consistent [5]. The questionnaire response rate was low among controls (884/8166), possibly affecting the generalizability of the study conclusion. Controls were better educated on average and may have better understood the meaning of this study and have been willing to participate as controls. However, the educational background of participants was adjusted in the statistical model. According to Yakult Honsha data, purchase of BLS was not associated with household income, which is generally correlated with educational background.

Daily consumption of BLS since adolescence had a significant inverse association with early breast cancer occurrence. A significant inverse association was also seen between consumption of soy isoflavones and breast cancer occurrence. The results are consistent with those from a case-control study conducted by Hirose and colleagues [11] in which the OR for premenopausal breast cancer in the highest tertile of soy isoflavone consumption against the lowest tertile was estimated at 0.44 (95% CI, 0.22–0.89). BLS consumption increases the NK cell activity and boosts the immune system in human [9]. A chemical carcinogenesis study in mice showed oral intake of *L. casei* Shirota inhibited carcinogenesis by enhancing the NK cell activity [19]. Increased NK cell activity and isoflavone metabolisms [20] are both potential underlying mechanisms of the breast cancer preventive effect of BLS. Soy isoflavones and their metabolites have been shown to prevent breast cancer, prostate cancer and osteoporosis in a number of epidemiological studies. Having a higher affinity for estrogen receptor β and a stronger antioxidative activity compared with other isoflavone derivatives, a daidzein metabolite equol plays an important role in cancer prevention [21, 22]. Recently, an increase in the population level of intestinal lactobacilli was shown to potentially activate the intestinal isoflavone metabolism [23, 24]. The analyses in this study suggested a biological interaction between BLS and soy isoflavones. Just as in women who consume more soy isoflavones, breast cancer may be prevented in women who consume BLS even if they consume little soy isoflavones. The interaction between the intestinal flora and the isoflavone metabolism may also be involved in the mechanism. Further studies are warranted.

So far no prospective study in human has evaluated how BLS consumption changes the intestinal flora and equol production. Now intestinal flora can be identified using an inexpensive new technology that produces results quickly, which is based on the reverse transcription-quantitative polymerase

Table 3. Crude and Adjusted Odds

	Case (n=306)	Control (n=662)	Crude Odds Ratio‡				Adjusted Odds Ratio*			
			OR	95%CI		p	OR	95%CI		p
Probiotic beverage										
<4 times	88.9%	83.8%	Reference.			0.061	Reference.			0.048
≥ 4 times	11.1%	16.2%	0.66	0.43	1.02		0.65	0.42	1.00	
Soy isoflavone										
Q1 (<18.76mg/day)	33.0%	24.9%	Reference.			0.0012**	Reference.			0.0002**
Q2 (18.76-<28.81mg/day)	25.8%	25.1%	0.74	0.49	1.10		0.76	0.52	1.13	
Q3 (28.81-<43.75mg/day)	21.6%	24.9%	0.58	0.38	0.88		0.53	0.35	0.81	
Q4 (43.75mg/day-)	19.6%	25.1%	0.52	0.34	0.79		0.48	0.31	0.73	

‡ Calculated using conditional logistic regression. 304 cases and 630 controls were matched for age and residential area. 2 cases and 32 controls were unmatched and excluded from the analysis.

* Calculated using conditional logistic regression. 306 cases and 661 controls were matched for residential area and adjusted for age (40s and 50s), educational background, physical activity level, benign mammary tumor, family breast cancer history, age at menarche, number of births, breastfeeding experience, use of female sex hormone before menopause, birth weight, Body Mass Index around the age of 20, smoking and energy intake. One control was excluded due to lack of adjustment factor.

** Trend P calculated from the linear score. (0=Q1, 1=Q2, 2=Q3, 3=Q4)

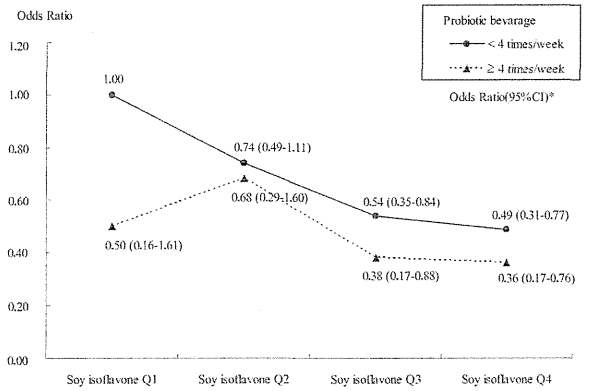

Fig. (2). Interaction between probiotic beverage and soy isoflavone consumption.

* Calculated using conditional logistic regression. 306 cases and 661 controls were matched for residential area and adjusted for age (40s and 50s), educational background, physical activity level, benign mammary tumor, family breast cancer history, menarche, number of births, breastfeeding, use of female hormone, birth weight, Body Mass Index around the age of 20, smoking and energy intake. One control was excluded due to lack of adjustment factor.

Table 4. Subgroup Analyses of Premenopausal Women and Postmenopausal Women

	Premenopausal Women						Postmenopausal Women					
	Case	Control	Adjusted Odds Ratio*				Case	Control	Adjusted Odds Ratio*			
	(n=195)	(n=462)	OR	95% CI		p	(n=111)	(n=200)	OR	95% CI		p
Probiotic beverage												
<4 times	88.2%	83.1%	Reference.			0.35	90.1%	85.5%	Reference.			0.046
≥ 4 times	11.8%	16.9%	0.78	0.46	1.32		9.9%	14.5%	0.43	0.19	0.99	

* Calculated using conditional logistic regression. Each subgroup was matched for residential area and adjusted for age (40s and 50s), educational background, physical activity level, benign mammary tumor, family breast cancer history, menarche, number of births, breastfeeding, use of female hormone, birth weight, Body Mass Index around the age of 20, smoking and energy intake. One control was excluded due to lack of adjustment factor in the analysis of premenopausal women.

chain reaction analysis of microbacterial rRNA in human feces [25]. This technology may be useful in future studies.

The stronger inverse association shown in our main analysis is consistent with the results of epidemiological studies showing an association between soy consumption in adolescence and decrease in breast cancer risk [26, 27] as well as the results of a breast cancer/prostate cancer prevention study in animals [28]. A subgroup analysis showed an inverse association between daily BLS consumption and breast cancer occurrence irrespective of menopausal status. The inverse association was strong and statistically significant in postmenopausal women.

5. CONCLUSION

This population-based case-control study in Japanese women showed an inverse association between BLS consumption since adolescence and breast cancer occurrence. Soy isoflavone consumption was also inversely associated with breast cancer occurrence as shown in the previous studies.

Despite the study design that did not allow to indicate the recommended amount of probiotic beverages and soy isoflavone for the prevention of breast cancer, our study results suggested the benefit of consuming these products. Further studies may be able to recommend the lifestyle modification with diet including consumption of BLS and soy isoflavone.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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ORIGINAL ARTICLE

A feasibility study of outpatient chemotherapy with S-1 + cisplatin in patients with advanced gastric cancer

Shunsuke Okazaki · Takako E. Nakajima · Jun Hashimoto · Seiichiro Yamamoto · Daisuke Takahari · Ken Kato · Tetsuya Hamaguchi · Yasuhide Yamada · Yasuhiro Shimada · Kenji Tamura

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Abstract
Background Regimens of standard-dose cisplatin have usually been administered as inpatient chemotherapy in Japan. This prospective study evaluated the feasibility of outpatient chemotherapy with standard-dose cisplatin in Japanese patients with advanced gastric cancer.
Methods Advanced gastric cancer patients received an S-1 + cisplatin regimen (S-1: 80–120 mg days 1–21; cisplatin: 60 mg/m^2 day 8, every 4–5 weeks), either as outpatient chemotherapy with oral hydration on days 9–10, or as inpatient chemotherapy with intravenous hydration on days 9–10, based on the results of an oral hydration test during days 1–7 of the first cycle. The primary endpoint was the completion rate of two cycles in the outpatient group.
Results A total of 36 patients were enrolled: 32 were allocated to the outpatient group and 4 to the inpatient group. The completion rate of two cycles in the outpatient group was 78% [90% confidence interval (CI): 63–89]. The median of the total number of treatment cycles of S-1 + cisplatin and the median progression-free survival in the outpatient group were 5 (range 1–11) and 10.6 months (95% CI 4.2–16.9), respectively. Although seven patients in the outpatient group discontinued treatment, mainly owing to gastrointestinal toxicity, most of them could continue S-1 + cisplatin by switching to inpatient chemotherapy from the next cycle.
Conclusion Outpatient chemotherapy with S-1 + cisplatin in advanced gastric cancer patients can be safely and effectively administered in Japan with appropriate patient selection and supportive treatment.

Keywords Cisplatin · Gastric cancer · Oral hydration · Outpatient chemotherapy · S-1

S. Okazaki · T. E. Nakajima · J. Hashimoto · K. Kato · T. Hamaguchi · Y. Yamada · Y. Shimada
Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, Japan

S. Okazaki
Department of Medical Oncology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

T. E. Nakajima · K. Tamura
Outpatient Chemotherapy Center, National Cancer Center Hospital, Tokyo, Japan

T. E. Nakajima (✉)
Department of Clinical Oncology, St. Marianna University, School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan
e-mail: tnakajima@marianna-u.ac.jp

S. Yamamoto
Statistics and Cancer Control Division, National Cancer Center, Tokyo, Japan

D. Takahari
Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Background

Gastric cancer is the most common cause of morbidity from cancer in Japan, and despite a decrease in recent years its mortality rate is still as high as 16% among all cancers [1]. Unresectable or recurrent gastric cancer has an extremely poor prognosis, so the establishment of a standard chemotherapy regimen is a high priority. Since the FAM-TX [5-fluorouracil (5-FU) + doxorubicin + methotrexate] regimen demonstrated a survival advantage over best

supportive care [2], various regimens have been developed around the world.

Although a 5-FU continuous infusion regimen had long been considered the standard in Japan for unresectable or recurrent gastric cancer, based on the results of the Japan Clinical Oncology Group (JCOG) 9205 trial [3], an S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate) + cisplatin (CDDP) regimen recently replaced it, on the basis of the JCOG 9912 trial [4] and SPIRITS trial [5], and this regimen is now widely used. In China, as well as in Japan, S-1 + CDDP is regarded as one of the standard treatments for unresectable or recurrent gastric cancer, based on the results of a domestic randomized controlled trial [6]. The FLAGS trial was conducted in Western countries to prove the superiority of S-1 + CDDP over 5-FU + CDDP, and S-1 + CDDP demonstrated better overall survival (although without statistical significance) and a significantly better safety profile [7].

Outpatient chemotherapy has gradually become popular in Japan with the spread of outpatient chemotherapy units [8]. However, regimens containing standard-dose CDDP ($\geq$50 mg/m^2) have usually been administered as inpatient chemotherapy because the regimen is highly emetic and requires intensive hydration [9], although it is commonly administered as outpatient chemotherapy in Western countries. According to a recent conference presentation in Japan, only 3.7% of chemotherapy with standard-dose CDDP was administered on an outpatient basis in Japan. The drug lag of new-generation antiemetics, plus delays in the development of antiemetic guidelines and in the improvement of the infrastructure of outpatient chemotherapy units, are other reasons for the high proportion of inpatient treatment. This situation decreases the quality of life of patients and imposes a large financial burden due to the hospitalization cost.

In recent years, some encouraging reports have emerged from Japan. A report on the safety data of a retrospective study in lung cancer patients who received standard-dose CDDP with a "short hydration regimen [10]", which was already common in Western countries, was presented at a recent meeting in Japan. However, it is assumed that oral hydration is unsuitable for advanced gastric cancer patients, due to their specific conditions, such as the stenosis caused by the primary lesion, anorexia in postgastrectomy patients, and potential bowel obstruction due to peritoneal dissemination. We performed a single-institute retrospective study in 45 advanced gastric cancer patients receiving S-1 + CDDP as the first-line treatment, and found that 15 patients (33%) with gastrointestinal toxicity of grade 1 or less for their entire treatment period could be potential candidates for safely receiving standard-dose CDDP as outpatient chemotherapy. This paper reports on a prospective study conducted to evaluate the feasibility of outpatient chemotherapy with S-1 + CDDP in advanced gastric cancer patients in Japan.

Patients and methods

Patients

Eligibility criteria were as follows: unresectable or recurrent gastric cancer, or advanced gastric cancer which required neoadjuvant chemotherapy with S-1 + CDDP; histologically confirmed gastric adenocarcinoma; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; aged between 20 and 75 years; agreed to take oral hydration of $\geq$1.5 L/day; and adequate organ functions: neutrophil count $\geq$1200/mm^3, hemoglobin level $\geq$8.0 g/dL, platelet count $\geq$75000/mm^3, total bilirubin level $\leq$3.0 mg/dL, and aspartate aminotransferase and alanine aminotransferase levels $\leq$100 IU/L. In terms of renal function, either a serum creatinine level of $\leq$1.5 mg/dL or an estimated creatinine clearance of $\geq$50 mL/min was required. Prior chemotherapy was allowed except for a CDDP-containing regimen, and measurable lesions were not mandatory. Although the conditions of patients with and without prior chemotherapy might have been different, we considered it allowable to include patients with prior chemotherapy (except for those who had received CDDP previously), because this study did not actually aim to prove the efficacy and safety of S-1 + CDDP.

Written informed consent was obtained from all patients, and the study was approved by the institutional review boards of each of the two institutions involved. The study was monitored for the entire time by an independent data and safety monitoring committee, and kept within the Helsinki Declaration and Japanese Ethical Guidelines for Clinical Studies. This study is registered with University hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), number 000002685.

Treatments

The study schema is shown in Fig. 1. S-1 was administered orally twice daily at a dose of 80–120 mg/day [80 mg/day for a body surface area (BSA) of <1.25 m^2, 100 mg/day for a BSA of 1.25–1.5 m^2, and 120 mg/day for a BSA of $\geq$1.5 m^2] for 21 consecutive days, followed by a 14-day rest; and CDDP was administered intravenously at a dose of 60 mg/m^2 on day 8. The protocol treatment was defined as two cycles, and we recommended continuing S-1 + CDDP as a subsequent treatment when it was effective. When administered as neoadjuvant chemotherapy, the rest period could be shortened to a minimum of 7 days. Patients were given an oral hydration test during

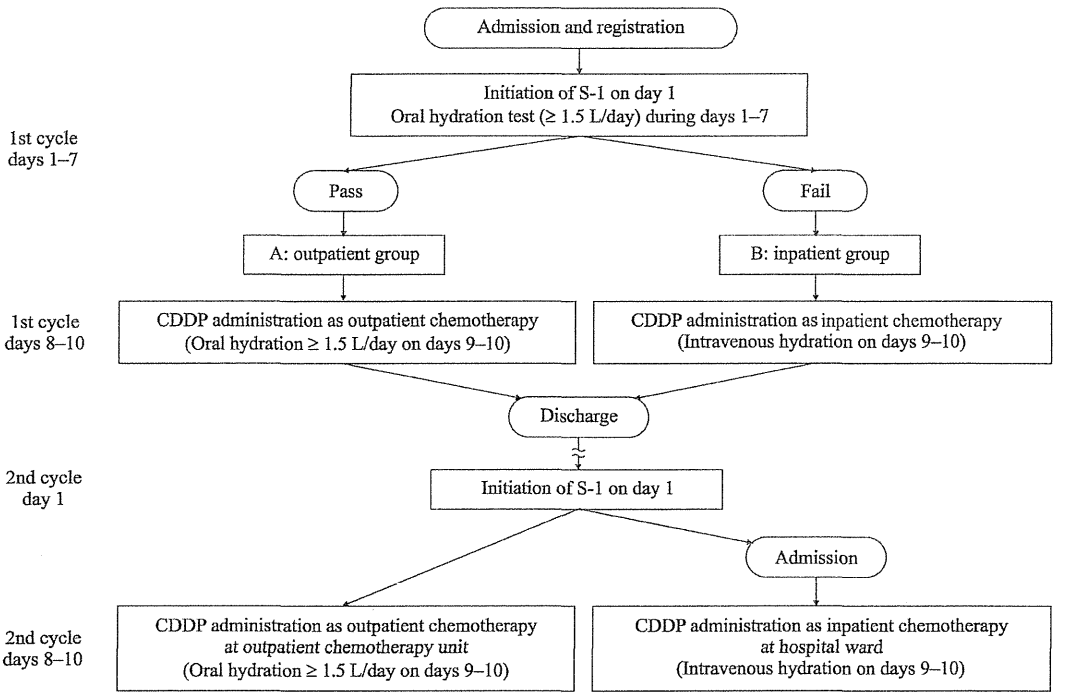

Fig. 1 Flow chart of protocol treatment. *CDDP* cisplatin

days 1–7 of the first cycle. In the oral hydration test, patients were required to take oral hydration of ≥1.5 L/day in addition to food every day throughout days 1–7. Patients wrote down the self-reported amount of oral hydration every day throughout days 1–7, and the physicians checked it by the next morning. Chemotherapy in the first cycle was initiated after hospital admission in every patient, to enable an accurate check of the amount of oral hydration. Patients were allocated to the outpatient group (group A) if they passed the oral hydration test (or if they could take oral hydration of ≥1.5 L/day every day throughout days 1–7), and they were allocated to the inpatient group (group B) if they failed the test. Group A patients were administered intravenous hydration only on day 8, and were encouraged to take oral hydration of ≥1.5 L/day on days 9–10. They were then discharged, and continued to take S-1 until day 21. In the second cycle they were not given an oral hydration test, and CDDP was administered at the outpatient chemotherapy unit on day 8. Group B patients were administered intravenous hydration of the same amount as group A patients on day 8 and 2 L/day on days 9–10, and CDDP was administered in the hospital ward on day 8 in the second cycle.

The CDDP administration method in group A is shown in Table 1. In group A, a total of 2300 mL hydration was administered in 5 h and 15 min. Patients were orally administered antiemetics on days 9–11 and diuretics when they gained weight by ≥1.5 kg in relation to their weight on day 8. Group B patients were administered these drugs intravenously. The regimen of antiemetics was in accordance with the 1999 American Society of Clinical Oncology (ASCO) guidelines [11], because newer agents such as aprepitant and palonosetron had not been approved in Japan when the study was being planned. Group A patients were required to contact their physicians immediately when they could not take adequate oral hydration on days

Table 1 Cisplatin administration method in group A

Day 8			
Normal saline	1000 mL	Drip infusion	2 hours
Dexamethasone Granisetron Normal saline	20 mg 1 mg 50 mL	Drip infusion	15 minutes
Cisplatin Normal saline	60 mg/m^2 250 mL	Drip infusion	1 hour
Normal saline	1000 mL	Drip infusion	2 hours
Days 9–10			
Oral hydration	≥ 1.5 L	Orally	
Days 9–11			
Dexamethasone Granisetron	16 mg 2 mg	Orally	
Furosemide	40 m	Orally (as needed)	

9–10, and they were administered intravenous hydration as needed, resulting in discontinuation of the protocol treatment. Even in these patients, S-1 + CDDP could be continued. The completion of treatment was defined as follows: had taken S-1 for ≥14 days per cycle, had been administered CDDP, and had not met the discontinuation criteria for S-1 + CDDP. Treatment discontinuation was required in any of the following cases: inadequate oral hydration despite a lack of major toxicity or intravenous hydration on days 9–10 (group A only), administration of second-cycle CDDP as inpatient chemotherapy at the physician's discretion (group A only), disease progression, unacceptable toxicity, patient's refusal, and physician's judgment.

Physical and blood examinations were required every week in the first cycle and every other week in the second cycle. The toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Imaging tests were performed after the completion of two cycles, and the response was evaluated with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 in those patients with measurable lesions.

Statistical analysis

The completion rates of two cycles in the SPIRITS trial and in our retrospective study were 70% (90% CI 63–76) and 78% (90% CI 65–87), respectively, as the first-line treatment in the hospital ward. Because the patients were recruited to this study regardless of their history of prior chemotherapy (except for those who had received CDDP previously), and CDDP was administered as outpatient chemotherapy in group A, a 50% completion rate of two cycles in group A was considered acceptable. Given that the point estimate was around 50%, and the 90% CI was between 30 and 70%, 20 patients were required in group A. Therefore, given that the proportion allocated to group A was around 60%, and in expectation of a few ineligible patients, the total sample size required was determined to be 35 patients.

The primary endpoint was the completion rate of two cycles in group A. The secondary endpoints were as follows: the completion rate of two cycles in group B, progression-free survival in each group, and adverse events in each group. Progression-free survival was defined as the period from the registration date to the earlier of the first radiological or clinical disease progression or death from any cause. In the event that neither disease progression nor death occurred, the case was censored at the last date confirmed as progression-free. When a patient in the neoadjuvant setting could subsequently receive curative surgery, the case was censored at the date of surgery.

A follow-up survey was scheduled 1 year from the date of the last registration. Progression-free survival was analyzed using the Kaplan–Meier method. All of the analyses were performed by an intention-to-treat method, using SAS version 9.2.

Results

A total of 36 patients were registered from two institutions in Japan between October 2008 and July 2009; 32 patients were allocated to group A and 4 to group B. Patient characteristics in each group are shown in Table 2. In terms of ECOG performance status, all the patients were either 0 or 1. In five patients the regimens were administered as neoadjuvant chemotherapy, and all five of these patients were allocated to group A. Seven patients (22%) in group A and one (25%) in group B had a history of prior chemotherapy (Table 3). The median follow-up period was 13.0 months (range 3.0–21.3).

The number of patients who completed the protocol treatment was 25 in group A, and 4 in group B. Therefore, the completion rate of two cycles was 78% (90% CI 63–89) in group A, and 100% (90% CI 47–100) in group B. Of the five patients who received S-1 + CDDP as neoadjuvant chemotherapy, two could receive curative surgery subsequently. Of the seven patients (22%) in group A who could not complete the protocol treatment, six could continue

Table 2 Patient characteristics

	Group A $N = 32$	Group B $N = 4$
Median age, years (range)	62 (34–75)	65 (59–75)
Sex		
Male	22	4
Female	10	0
ECOG performance status		
0	13	1
1	19	3
Treatment line		
Neoadjuvant chemotherapy	5	0
First line	20	3
Second line	4	1
Third line	3	0
Primary lesion		
Yes	27	2
No	5	2
Peritoneal metastasis		
Yes	20	3
No	12	1

ECOG Eastern Cooperative Oncology Group

S-1 + CDDP as inpatient chemotherapy from the next cycle, whereas one was forced to switch to S-1 monotherapy due to grade 3 anorexia, nausea, and diarrhea.

Adverse events in each group are shown in Table 4. In regard to the elevation of the serum creatinine level in group A, creatinine of all-grade and grade 3–4 was found in 14 patients (44%) and none (0%), respectively. All-grade creatinine promptly resolved in most patients: it was still found only in 5 patients (16%) at the completion of the second cycle, and in the same number at the completion of the S-1 + CDDP regimen. There were no treatment-related deaths or early deaths within 30 days after treatment discontinuation.

In group A, delay in initiation of the second cycle due to adverse events occurred in six patients (19%), dose reduction related to adverse events was required in five patients (16%), and treatment discontinuation was required in seven patients (22%) for the following reasons: six had severe gastrointestinal toxicity, and one had inadequate oral hydration on days 9–10 despite a lack of major toxicity.

The median of the total number of treatment cycles of S-1 + CDDP, including subsequent treatment after the third cycle, was 5 (range 1–11) in group A, and 5 (range 2–7) in group B. Median progression-free survivals in group A and B were 10.6 months (95% CI 4.2–16.9) and 5.6 months (95% CI 1.7–9.5), respectively (Fig. 2).

Table 3 Prior chemotherapy

	Group A $N = 32$	Group B $N = 4$
First line		
S-1 monotherapy	5	1
5-FU continuous infusion	1	0
5-FU + methotrexate	1	0
Second line		
NK105 (micelle product of paclitaxel)	3[a]	0

5-FU 5-fluorouracil

[a] All patients received S-1 monotherapy as first line

Discussion

In the present study, the completion rate of two cycles in group A was 78% (90% CI 63–89), and this met the predefined threshold. In addition, all the other endpoints, as well as the median of the total number of treatment cycles of S-1 + CDDP, were equal to or better than those found in previous reports [5, 12].

Based on these positive results in both groups, we conclude that outpatient chemotherapy with standard-dose CDDP in advanced gastric cancer patients is feasible, and that an oral hydration test has the potential to be appropriate for patient selection into outpatient chemotherapy or inpatient chemotherapy. To our knowledge, this is the first prospective study in Japan to have proven that outpatient chemotherapy with standard-dose CDDP can be performed safely.

The major reason for treatment discontinuation in the seven patients in group A was severe gastrointestinal toxicity. We could not find major differences in patient characteristics between those who could and those who could

Table 4 Adverse events

CTCAE v 3.0	Group A $N = 32$		Group B $N = 4$	
	All grades N (%)	Grades 3–4 N (%)	All grades N (%)	Grades 3–4 N (%)
Leukocytes	23 (72)	3 (9)	3 (75)	0 (0)
Neutrophils	14 (44)	7 (22)	3 (75)	0 (0)
Hemoglobin	32 (100)	2 (6)	3 (75)	0 (0)
Platelets	13 (41)	0 (0)	2 (50)	0 (0)
Febrile neutropenia	1 (3)	0 (0)	0 (0)	0 (0)
Infection with normal ANC	2 (6)	1 (3)	0 (0)	0 (0)
Creatinine	14 (44)	0 (0)	0 (0)	0 (0)
Fatigue	20 (63)	0 (0)	3 (75)	0 (0)
Anorexia	27 (84)	4 (13)	4 (100)	0 (0)
Nausea	22 (69)	2 (6)	3 (75)	0 (0)
Vomiting	7 (22)	1 (3)	1 (25)	0 (0)
Stomatitis	17 (53)	0 (0)	2 (50)	0 (0)
Diarrhea	17 (53)	3 (9)	2 (50)	0 (0)
Constipation	15 (47)	0 (0)	2 (50)	0 (0)

CTCAE Common Terminology Criteria for Adverse Events, *v* version, *ANC* absolute neutrophil count

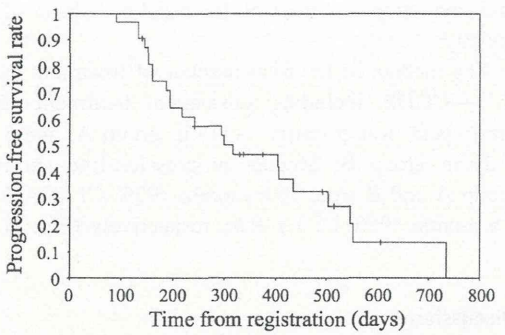

Fig. 2 Progression-free survival in group A

not complete the protocol treatment, and it is difficult to predict such toxicities in advance. Six out of these seven patients in group A were able to continue S-1 + CDDP by switching to inpatient chemotherapy from the next cycle. In addition, another two patients who completed the protocol treatment could also continue it by switching to inpatient chemotherapy in their subsequent treatment. Of the 31 patients in group A who received not less than two cycles of S-1 + CDDP, 23 patients stayed in group A for the entire time and 8 moved to group B subsequently. The proportion of any toxicity of grade 3 or more was 13% in patients who stayed in group A, and 38% in patients who moved to group B, indicating a certain level of difference; however, almost all the patients who moved to group B experienced these severe toxicities during the treatments in group A, not after they moved to group B. In addition, all-grade creatinine (39 and 25%), median progression-free survival (7.0 and 8.0 months), and the median of the total number of treatment cycles of S-1 + CDDP (4 and 5) were all comparable in these two subgroups: patients who stayed in group A and those who moved to group B. This study therefore also proved that S-1 + CDDP can be safely continued even if it is initiated as outpatient chemotherapy and subsequently has to be switched to inpatient chemotherapy.

The present study has several limitations. Firstly, we prospectively examined only two cycles as the protocol treatment. This is because we included patients in the neoadjuvant setting in the target population, and we usually give such patients no more than two cycles of S-1 + CDDP. However, the median of the total number of treatment cycles of S-1 + CDDP was equal to or better than that found in previous reports [5, 12], so we do not consider this to be a major issue.

Secondly, there is insufficient evidence for the adequacy of the specified volume, 1.5 L/day, of oral hydration we used, both during the period of the oral hydration test and on days 9–10. To our knowledge, there has been no randomized controlled trial to determine an adequate infusion volume on the day of CDDP administration, and there is far less evidence for the amount of oral hydration required before or after the day of CDDP administration. A report on the pharmacokinetics of CDDP showed that the blood level of free CDDP, which causes renal toxicity, diminished below the limit of detection sensitivity on the day after CDDP administration [13], and it is thought that hydration on the day after CDDP administration may not be indispensable.

Thirdly, the regimen of antiemetics we used was outdated because of the drug-lag of approval of new-generation antiemetics in Japan. Aprepitant was finally approved in Japan in October 2009 and palonosetron was approved in January of 2010.

Outpatient chemotherapy with standard-dose CDDP in Japan can also be justified from a cost standpoint. According to the estimate at our institution, the treatment cost per cycle was JPY 131,834 in group A (fee-for-service and drug cost for three visits) and JPY 317,860 in group B (fee-for-service for two visits and Diagnosis Procedure Combination cost for 6-day hospitalization). The cost of outpatient chemotherapy administration in group A was therefore as low as 42% of that of the inpatient administration in group B.

This finding does not mean we ought to force outpatient chemotherapy on those who do not want to accept oral hydration, or those who strongly desire to receive inpatient chemotherapy. However, we should keep in mind that many more patients prefer outpatient chemotherapy to inpatient chemotherapy [14, 15], even when the regimen contains standard to highdose CDDP [16]. Also, it may be possible to give outpatient chemotherapy from the first cycle without an oral hydration test for patients who agree to take oral hydration of $\geq$1.5 L/day, because of improvements in antiemetics compared with those used before. One important point to note is that timely switching from outpatient chemotherapy to inpatient chemotherapy should be considered for patients with any severe gastrointestinal toxicity or inadequate oral hydration.

In conclusion, outpatient chemotherapy with S-1 + CDDP in advanced gastric cancer patients can be safely and effectively performed in Japan with appropriate patient selection and supportive treatment. However, the long period of infusion (more than 5 h) on the day of CDDP administration is a major issue. Further improvement in outpatient chemotherapy units is essential to allow the general use of outpatient chemotherapy with standard-dose CDDP in Japan.

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Conflict of interest None declared.

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ORIGINAL ARTICLE

Randomized trial of chemoradiotherapy and adjuvant chemotherapy with nimustine (ACNU) versus nimustine plus procarbazine for newly diagnosed anaplastic astrocytoma and glioblastoma (JCOG0305)

Soichiro Shibui · Yoshitaka Narita · Junki Mizusawa · Takaaki Beppu · Kuniaki Ogasawara · Yutaka Sawamura · Hiroyuki Kobayashi · Ryo Nishikawa · Kazuhiko Mishima · Yoshihiro Muragaki · Takashi Maruyama · Junichi Kuratsu · Hideo Nakamura · Masato Kochi · Yoshio Minamida · Toshiaki Yamaki · Toshihiro Kumabe · Teiji Tominaga · Takamasa Kayama · Kaori Sakurada · Motoo Nagane · Keiichi Kobayashi · Hirohiko Nakamura · Tamio Ito · Takahito Yazaki · Hikaru Sasaki · Katsuyuki Tanaka · Hideaki Takahashi · Akio Asai · Tomoki Todo · Toshihiko Wakabayashi · Jun Takahashi · Shingo Takano · Takamitsu Fujimaki · Minako Sumi · Yasuji Miyakita · Yoichi Nakazato · Akihiro Sato · Haruhiko Fukuda · Kazuhiro Nomura

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Abstract

Purpose Glioblastoma (GBM) is one of the worst cancers in terms of prognosis. Standard therapy consists of resection with concomitant chemoradiotherapy. Resistance to nimustine hydrochloride (ACNU), an alkylating agent, has been linked to methylguanine DNA methyltransferase (MGMT). Daily administration of procarbazine (PCZ) has been reported to decrease MGMT activity. This study investigated the efficacy of ACNU + PCZ compared to ACNU alone for GBM and anaplastic astrocytoma (AA).

Methods Patients (20–69 years) who had newly diagnosed AA and GBM were randomly assigned to receive radiotherapy with ACNU alone or with ACNU + PCZ. The primary endpoint was overall survival (OS). This was designed as a phase II/III trial with a total sample size of 310 patients and was registered as UMIN-CTR C000000108.

Results After 111 patients from 19 centers in Japan were enrolled, this study was terminated early because temozolomide was newly approved in Japan. The median OS and median progression-free survival (PFS) with ACNU alone ($n = 55$) or ACNU + PCZ ($n = 56$) in the

S. Shibui (✉) · Y. Narita · Y. Miyakita · K. Nomura
Department of Neurosurgery and Neuro-Oncology,
National Cancer Center Hospital, 5-1-1,
Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: sshibui@ncc.go.jp

J. Mizusawa · A. Sato · H. Fukuda
Japan Clinical Oncology Group Data Center,
National Cancer Center, Tokyo, Japan

T. Beppu · K. Ogasawara
Department of Neurosurgery, Iwate Medical University,
Iwate, Japan

Y. Sawamura · H. Kobayashi
Department of Neurosurgery, Hokkaido University Graduate
School of Medicine, Hokkaido, Japan

R. Nishikawa · K. Mishima
Department of Neuro-Oncology/Neurosurgery,
International Medical Center, Saitama Medical University,
Saitama, Japan

Y. Muragaki · T. Maruyama
Department of Neurosurgery,
Tokyo Women's Medical University, Tokyo, Japan

J. Kuratsu · H. Nakamura · M. Kochi
Department of Neurosurgery,
Kumamoto University,
Kumamoto, Japan

Y. Minamida · T. Yamaki
Department of Neurosurgery,
Sapporo Medical University,
Sapporo, Japan

T. Kumabe · T. Tominaga
Department of Neurosurgery,
Tohoku University School of Medicine, Miyagi, Japan

T. Kayama · K. Sakurada
Department of Neurosurgery, Faculty of Medicine,
Yamagata University, Yamagata, Japan