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Review article

Paclitaxel chemotherapy for the treatment of gastric cancer

JUNICHI SAKAMOTO[1], TAKANORI MATSUI[2], and YASUHIRO KODERA[3]

[1]Department of Young Leaders' Program in Medical Administration, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan
[2]Department of Surgery, Aichi Cancer Center, Aichi Hospital, Okazaki, Japan
[3]Department of Digestive Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Abstract
A comprehensive review of phase I and phase II clinical trials of paclitaxel and paclitaxel-containing chemotherapy regimens for advanced gastric cancer was performed. Response rates, median progression-free survivals, and median overall survivals were examined, together with the treatment regimens and the numbers of patients registered in each trial. Although paclitaxel monotherapy produced considerable improvement in tumor response and prognosis, combination doublet or triplet chemotherapy with fluoropyrimidines and/or platinum compounds showed better results than the paclitaxel monotherapy. With regard to the schedule of paclitaxel administration, weekly injection seemed to show less toxicity and better results than administration every 3 weeks. Adjuvant therapies, chemoradiation therapies, and paclitaxel treatment for gastric ascites were also investigated and are discussed.

Key words Paclitaxel · Gastric cancer · Chemotherapy

Introduction

Gastric cancer is one of the most common types of solid tumor, and it is estimated to be the fourth most common in terms of morbidity, and the second most frequent cause of cancer death in the world [1]. Gastric cancer is particularly common in Asia, eastern Europe, and in South America, where the preservation of food is mostly performed by submerging it into salt, and where the detection rate of *Helicobactor pylori* is considerably high.

In Japan, where a vast store of data is available because of the long-term effort of the Gastric Cancer Registry, gastric cancer is the second most common cause of cancer mortality. Although the incidence of gastric cancer has been declining in most developed countries, esophago-gastric junctional tumor and tumor in the cardia has, conversely, been increasing [2] and these tumors still remain one of the biggest problems worldwide.

The prognosis of patients with advanced (i.e., unresectable or metastatic) gastric cancer is very poor. The median survival time for such patients is 6 to 9 months [3]. For many years, various chemotherapeutic agents have been used in attempts to improve survival, progression free-survival, response rate, and quality of life in patients with advanced gastric cancer as well as to improve disease-free survival in patients in whom curative resection of the cancers has been performed. 5-Fluorouracil (5-FU) and cisplatin-based regimens have long been considered reference treatments. Commonly used regimens have included epirubicin, cisplatin, and continuous infusion of 5-FU; 5 days' infusion of 5-FU plus cisplatin every 4 weeks; a weekly infusion regimen of 5-FU/leucovorin (LV) over 24 h plus cisplatin every 2 weeks; and 5-FU bolus plus 22-h infusion of 5-FU on days 1 and 2, in combination with cisplatin every 2 weeks. The results with these regimens, together with other study results, suggested that combination regimens including fluorinated pyrimidines, cisplatin, doxorubicin, epirubicin, and methotrexate, had better response rates than single agents. Although gastric cancer is a relatively chemosensitive disease, with response rates of 30% to 40%, these treatments have shown a modest but unsatisfactory increase in overall survival [4]. In this regard, chemotherapy in the advanced gastric cancer setting is limited by a low complete response rate, response durations that are short-lived, and considerable toxicities.

Nevertheless, recently, the development of new chemotherapeutic and molecular targeting agents has opened the door to various clinical trials to find novel therapeutic strategies to improve the outcome of

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patients with gastric cancer. Among such newly developed chemotherapeutic agents, paclitaxel has emerged as one of the most powerful compounds. Paclitaxel has activity against a broad range of tumor types, including breast, ovarian, lung, and head and neck cancers. Paclitaxel is also assumed to have activity in other malignancies that are refractory to conventional, first-line standard chemotherapies.

In this review, we focus on the activity of paclitaxel against advanced gastric cancers mainly through evidence-based medicine-oriented clinical trial results, and we evaluate the efficacy of combination chemotherapies, neoadjuvant and adjuvant chemotherapies, and multidisciplinary treatment with radiation therapy using paclitaxel.

Cytological and genetic reactions of paclitaxel in cancer cells

Paclitaxel, one of the taxanes, represents a new type of agent having both a specific chemical structure and mechanism of action.

Paclitaxel was discovered as part of the National Cancer Institute (NCI) national program in which thousands of plants, bacteria, and fungi were screened for the presence of anticancer activity. A crude extract from the bark of the Pacific yew, *Taxus brevifolia*, a slow-growing evergreen found in the Pacific northwest, proved to have cytotoxic activity against many cancer cells. Paclitaxel was obtained from the extract of the plant as an active constituent against cancer [5]. Although the development of paclitaxel was first disturbed by the scarce drug supply obtained from scarce natural products, semisynthetic replacement from other inactive precursor taxanes provided more abundant supplies.

Paclitaxel is an alkaloid ester consisting of a taxane ring system linked to a four-membered oxetan ring at positions C-4 and -5 (Fig. 1). Paclitaxel promotes the polymerization of tubulin, the principal function of tubulin being the formation of the mitotic spindle during cell division. Microtubules formed in the presence of paclitaxel are firmly stable and dysfunctional, thereby disrupting the normal microtubule dynamics required for cell division and interphase processes [6, 7]. Paclitaxel also induces the cellular process that leads to apoptosis or programmed cell death, even at doses that do not induce tubulin polymerization. Although the precise mechanism of this effect of paclitaxel has not yet been determined, cells exit from mitosis but do not continue to divide, and then substantial DNA fragmentation, indicative of apoptosis, leads to cell death in 2 to 3 days [8, 9]. The induction of tumor necrosis factor-α (*TNF-α*) gene expression is also caused by the action of paclitaxel, unrelated to its effect on microtubule assembly, raising the issue that this cytokine is related to the antitumor activity of paclitaxel [10]. This effect was not observed with other taxanes, such as docetaxel, although the clinical consequences of these differences have not been determined.

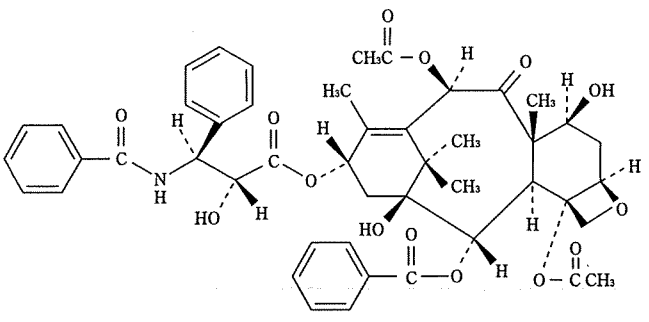

Fig. 1. The chemical structure of paclitaxel

Two mechanisms of acquired resistance to paclitaxel have been elucidated. First, mutations of tubulin isotype genes were reported to be a strong determinant of paclitaxel resistance in patients with non-small cell lung cancer [11]. Alterations in tubulin content, expression of tubulin isotype, and polymerization dynamics are considered to be related to resistance to paclitaxel [9]. The second mechanism of acquired resistance to paclitaxel involves the amplification of membrane phosphoglycoproteins that function as drug-efflux pumps [12]. The multidrug-resistant phenotype of tumor cells confers varying degrees of cross-resistance to various agents, including anthracyclines, etoposide, vinca alkaloids, colchicine, and taxanes. Resistance to paclitaxel can be reversed by many types of drugs, including calcium channel blockers, tamoxifen, cyclosporin A, antiarrythmic agents, and principal components of the vehicles used to formulate paclitaxel (cremophor EL) [13]. Several pathways that are involved in apoptosis during development and tumorigenesis, and critical genes in the regulation of these pathways have recently been discovered, e.g., *bcl-2, bcl-x, p53,* and *bax* [14]. Regulation of these apoptosis-related genes may also be involved in the regulation of paclitaxel-induced cytotoxicity and resistance [15].

Toxicities of paclitaxel during cancer therapy

Hypersensitivity reactions

The major hypersensitivity reactions to paclitaxel are dyspnea, bronchospasm, urticaria, and hypotension. These reactions usually occur within 2 to 3 min after the initiation of treatment and are almost noted within the first 10 min. Most of them occur with the first or second

drug administration. These hypersensitivity reactions resolve completely after the paclitaxel infusion is stopped and treatment with histamine receptor antagonists, fluids, and vasopressors is given. Minor hypersensitivity reactions, such as flushing and rashes, have also been noted in as many as 40% of patients. Premedication with corticosteroids and/or H_1, H_2 antagonists decreases the incidence of major hypersensitivity reactions to 1% to 3%.

Hematological toxicity

Neutropenia is the principal hematological toxic effect of paclitaxel. The onset is usually on days 8–10 after treatment and recovery is usually complete by 2 to 3 weeks. The neutropenia is not cumulative, suggesting that paclitaxel does not irreversibly damage immature hematopoietic cells. In most patients, the maximum tolerated dose of paclitaxel without granulocyte colony-stimulating factor is 175–200 mg/m^2 when the drug is administered every 3 weeks. Paclitaxel alone rarely causes thrombocytopenia or anemia.

Neurotoxicity

Peripheral neuropathy characterized by sensory symptoms such as numbness and paresthesia, in a glove-and-stocking-like distribution, is the principal neurotoxic effect of paclitaxel [16]. Severe neurotoxicity precludes a long-term treatment schedule with paclitaxel. The incidence of neurotoxicity has been particularly high in patients who receive paclitaxel as a 3-h infusion, suggesting that peak concentration may be a principal pharmacological determinant. Neurotoxicity seems to occur more frequently and is more serious when paclitaxel is administered in combination with cisplatin. There is no convincing evidence that any specific measure is effective at ameliorating existing manifestations or preventing the development or worsening of the neurotoxicity [17]. Optic nerve disturbances, characterized by scintillating scotomas, may occur in some patients [18].

Muscle toxicity

Transient myalgia, usually noted 2 to 5 days after therapy, is common at paclitaxel doses of 170 mg/m^2 or more, and myopathy is reported with high doses (250 mg/m^2) in combination with cisplatin. Nonsteroidal anti-inflammatory agents are used for palliating and preventing symptoms and narcotics are recommended to be administered prophylactically on days 2 to 5 after treatment in patients who have been symptomatic. Antihistamines have also been reported to be useful in preventing acute myalgia [19].

Cardiac toxicity

The most common cardiovascular symptom with paclitaxel is transient asymptomatic bradycardia, which is noted in 29% of patients [20]. Isolated cardiac bradycardia without hemodynamic effects is not an indication for discontinuing paclitaxel chemotherapy. More important bradyarrythmias and third-degree heart block have also been noted, but the incidence is around 0.1%. Routine cardiac monitoring during paclitaxel therapy is not necessary for most patients, except for those who have the complication of ventricular dysfunction.

Paclitaxel chemotherapy for advanced gastric cancer

Administration of paclitaxel every 3 weeks (3-weekly)

Because complete cure of advanced gastric cancer has not been achieved, the therapeutic goals are the control of disease progression, the relief of symptoms, improvement of quality of life, and the prolongation of survival. Paclitaxel has shown encouraging activity in the treatment of patients with advanced gastric cancer. Historically, paclitaxel has been administered as a bolus infusion every 3 weeks. Monotherapy with paclitaxel in the first-line treatment of advanced disease, as well as in the second-line setting, has produced response rates of approximately 17%-28% [21–24], and considerably longer survival times (median survival time [MST] around 8 months; Table 1) than those seen for other agents with similar response rates. It is the appreciable activity seen in these early phase II studies, along with the lack of cross-resistance to other drugs and the non-overlapping toxicities, that have led researchers to consider further development of the taxanes in combination with existing fluoropyrimidine-platinum regimens in advanced gastric cancer.

In order to improve the results, various combination therapies have been examined in clinical trials. Especially, paclitaxel appears to have a schedule-dependent synergy with platinum compounds, as documented in established human gastric cancer cell lines [25]. This synergy has led to the development of paclitaxel-platinum combination regimens in a number of solid tumors, including gastric cancer. Various phase II studies of 3-weekly paclitaxel-containing combinations in the treatment of patients with advanced gastric cancer are listed in Table 2 [26–41]. Combination regimens of paclitaxel plus platinum, or paclitaxel plus 5-FU, or both, yielded response rates of 32%-65% and MSTs of approximately 11 months (range, 6–14 months) in a first-line treatment setting. With regard to the patients in a setting of more than second-line treatment, the response rates were 22%-28% and median survival

Table 1. Phase II studies of every-3-weeks (3-weekly) paclitaxel monotherapy in advanced and metastatic gastric cancer

Study	Year	Treatment	*n*	Target population	RR (%)	Median progression-free survival (months)	Median survival time (months)
Cascinu et al. [21]	1998	P: 225 mg/m^2 over 3 h	36	Second-line	22	5	8
Ajani et al. [22]	1998	P: 200 mg/m^2 over 3 h	33	First-line	17	6.5	8
Yamada et al. [23]	2001	P: 210 mg/m^2 over 3 h	60	First-line, 34 Prior adjuvant chemotherapy, 6 Second-line, 26	23	5.1	11.3
Yamaguchi et al. [24]	2002	P: 210 mg/m^2 over 3 h	32	First-line, 15 Prior adjuvant chemotherapy, 4 Second-line, 17	28	3	8

n, number of patients; P, paclitaxel; RR, response rate

Table 2. Phase II studies of 3-weekly paclitaxel-containing combinations in advanced and metastatic gastric cancer

Study	Year	Treatment	*n*	Line of treatment	RR (%)	Median progression-free survival (months)	Median survival time (months)
Bokemeyer et al. [26]	1997	P: 175 mg/m^2 F: 2000 mg/m^2 L: 500 mg/m^2	22	First-line	32	8	11
Kim et al. [28]	1999	P: 175 mg/m^2 F: 750 mg/m^2 C: 20 mg/m^2	41	First–line 36 Prior adjuvant chemotherapy 3 Second line 5	51	4 (Median duration of response)	6
Murad et al. [27]	1999	P: 175 mg/m^2 F: 1500 mg/m^2	31	First line	66	9 (Median duration of response)	12
Kollmansberger et al. [29]	2000	P: 175 mg/m^2 F: 2000 mg/m^2 L: 500 mg/m^2 C: 50 mg/m^2	45	First line	51	9	14
Statpoulos et al. [30]	2002	P: 175 mg/m^2 Cb: 5 AUC	47	>Second-line	28	NR	NR
Gadgeel et al. [31]	2003	P: 200 mg/m^2 Cb: AUC 5	27	First-line	33	4.9 (Median duration of response)	7.5
Park et al. [32]	2004	P: 175 mg/m^2 C: 75 mg/m^2	36	First-line	46	4.9	13.8
Chang et al. [33]	2005	P: 200 mg/m^2 Cb: AUC 6	45	>Second-line	22	3.3	7.5
Shin et al. [34]	2005	P: 175 mg/m^2 C: 70 mg/m^2	34	First-line, 24 Second-line, 10	27	6.0	8.9
Lee et al. [35]	2005	P: 145 mg/m^2 C: 60 mg/m^2	39	First-line	44	4.7	12.1
Park et al. [36]	2006	P:175 mg/m^2 F: 500 mg/m^2	38	First-line Prior adjuvant chemotherapy, 11	42	4.3	9.9
Lee et al. [37]	2007	P: 145 mg/m^2 C: 60 mg/m^2	32	Second-line	25	2.9	9.1
Im et al. [38]	2008	P: 175 mg/m^2 F: 1000 mg/m^2 L: 20 mg/m^2	60	First-line 37 Prior adjuvant chemotherapy 13 Second-line 23	32	3.0	14.0
Kang et al. [39]	2008	P: 175 mg/m^2 X: 825 mg/m^2	45	First-line Prior adjuvant chemotherapy 9	49	5.6	11.3
Hwang et al. [40]	2008	P: 175 mg/m^2 C: 75 mg/m^2 F: 750 mg/m^2	45	First-line Prior adjuvant chemotherapy 13	51	6.9	12.7
Jung et al. [41]	2009	P: 135 mg/m^2 C: 30 mg/m^2 F: 1200 mg/m^2 L: 20 mg/m^2	30	NR	46	5.6	9.6

n, number of patients; AUC, area under the concentration-time curve; C, cisplatin; Cb, carboplatin; F, 5-FU; L, folinic acid (LV); P, paclitaxel; X, capecitabine; RR, response rate; NR, not reported

ranged from 6 to 10 months. Although these studies differed with respect to drug regimens and populations treated, the regimens were generally well tolerated, with myelosuppression as the most common toxicity. Other reported toxicities associated with these combination therapies were alopecia, myalgia, mucositis, and neurotoxicity.

The effect of paclitaxel in these combination regimens was obvious, in terms of response rates and MST, compared to paclitaxel monotherapy when the regimens were utilized in a first-line setting. However, in the second-line setting, the combination chemotherapies did not show clear survival benefits compared to the administration of paclitaxel alone.

Weekly administration of paclitaxel

Phase II trials have suggested that weekly paclitaxel may be more effective and less toxic than every-3-week administration for metastatic breast cancer. The Cancer and Leukemia Group B protocol 9840 was initiated to address this question in a phase III trial. The final result was published in 2008, and it was confirmed that weekly paclitaxel administration was superior to an every-3-weeks (3-weekly) paclitaxel schedule for metastatic breast cancer, with a significant increase in response rate and an important advantage in time to progression [42]. Inspired by the results of these studies, studies of weekly paclitaxel, together with various paclitaxel-containing combinations with other chemotherapeutic agents, have been performed for the treatment of advanced gastric cancer.

Monotherapy with weekly paclitaxel in the first-line treatment of advanced disease, as well as in the second-line setting, has produced response rates of approximately 16%-18% and MSTs of around 8 months (Table 3) [43, 44] that were almost identical to the results of 3-weekly administration. However, the quality of life of the patients, and compliance with the study regimens, seemed to be better for weekly administration than for the 3-weekly administration regimen.

Many phase II studies have also been performed to investigate the safety profile and effectiveness of weekly paclitaxel-containing combination therapies for advanced and metastatic gastric cancers (Table 4) [45–61].

Combination therapies with 5-FU+leucovorin or 5-FU were examined in three trials [46, 50, 61]. The addition of either bolus 5-FU (2400–2600 mg/m^2) or 5 days' continuous infusion of 600 mg/m^2 5-FU to weekly paclitaxel at 80 mg/m^2 was proven not to affect the safety of the patients [62]. Response rates ranged from 39% to 41% and median progression-free survival time was more than 3.5 months in all these studies. The MST was also improved, from 8.8 to 11.0 months, suggesting that the combination of weekly paclitaxel with 5-FU is superior to weekly paclitaxel monotherapy in terms of response rate and prognosis.

Weekly paclitaxel combined with cisplatin has also been investigated [51, 52, 54]. Weekly administration of paclitaxel 80 mg/m^2 with weekly cisplatin at 25 mg/m^2 did not show any additional toxicity compared with that of weekly paclitaxel monotherapy [63]. Although the response rates of these regimens varied, from 18% to 41%, the combination of weekly or biweekly paclitaxel with cisplatin showed an improved prognosis of around 11 months.

Combination triplet therapy using paclitaxel, 5-FU, and cisplatin was also studied [45, 53]. Although this type of regimen demonstrated high response rates, of around 50%, median survival was around 11 months, and was not very much improved compared to that with doublet paclitaxel-5-FU regimens or paclitaxel-cisplatin regimens. A new phase II trial is now under way, according to the recommended dose of weekly paclitaxel 80 mg/m^2, cisplatin 25 mg/m^2, and 5-FU 600 mg/m^2, that was suggested by a high response rate of 83% in a phase I trial [64].

With regard to oral chemotherapeutic agents, weekly paclitaxel combined with oral UFT (uracil, tegafur) plus leucovorin showed a response rate of 50% and MST of 9.8 months [48]. Studies of combinations with oral S-1 (tegafur, gimeracil, oteracil) have also been performed [47, 49, 55–59]. In these trials, response rates ranged from 40% to 65% and MSTs ranged from 8.9 to 15.5 months. Weekly administration of 40–60 mg/m^2 paclitaxel combined with 80 mg/m^2 of S-1 for 14 days in a 4-week cycle [65] seemed to have superior benefit in terms of prognosis (median, 13.85 months) compared to

Table 3. Phase II studies of weekly paclitaxel monotherapy in advanced and metastatic gastric cancer

Study	Year	Treatment	*n*	Line of treatment	RR (%)	Median progression-free survival (months)	Median survival time (months)
Kodera et al. [43]	2007	P: 80 mg/m^2/week > 3/4 weeks	45	Second-line	16	2.6	7.8
Emi et al. [44]	2008	P: 80 mg/m^2/week > 3/4 weeks	68	First-line	17.6	3.2	7.3

n, number of patients

Table 4. Phase II studies of weekly (w) or biweekly (2 w) paclitaxel-containing combinations for advanced and metastatic gastric cancer

Study	Year	Treatment	*n*	Line of treatment	RR (%)	Median progression-free survival (months)	Median survival time (months)
Honecker et al. [45]	2002	P: 80 mg/m^2 (w) F: 2000 mg/m^2 L: 500 mg/m^2 C: 50 mg/m^2	29	First-line	48	8	11
Yeh et al. [46]	2005	P: 80 mg/m^2 (w) F: 2600 mg/m^2 L: 300 mg/m^2	30	First-line Prior adjuvant chemotherapy 2	41	6	10
Mochiki et al. [47]	2006	P: 60 mg/m^2 (w) S: 80 mg/m^2	24	First-line Prior adjuvant chemotherapy 4	54	9.5	15.5
Chao et al. [48]	2006	P: 100 mg/m^2 (w) U:300 mg/m^2 L: 90 mg/m^2	55	First-line Prior adjuvant chemotherapy 2	50	4.4	9.8
Kawabata et al. [49]	2007	P: 50 mg/m^2 (w) S: 80 mg/m^2	18	First-line	65	9.1	13.8
Ninomiya et al. [50]	2007	P: 80 mg/m^2 (w) F: 600 mg/m^2	57	First-line 32 Second-line 25	39	5.4	11
Kim et al. [51]	2007	P: 140 mg/m^2 (2 w) C: 30 mg/m^2	50	First-line 35 Second-line 15	18	2.9	11.1
Kim et al. [52]	2007	P: 100 mg/m^2 (w) C: 35 mg/m^2	52	First-line	36.5	6.0	10.8
Gu et al. [53]	2008	P: 60 mg/m^2 (w) F: 500 mg/m^2 C: 75 mg/m^2	46	First-line	50	5.6	10.8
Nagata et al. [54]	2008	P: 80 mg/m^2 (w) C: 25 mg/m^2	49	First-line 25 Second-line 24	41	5.5	10.9
Nakajo et al. [55]	2008	P: 120 mg/m^2 (2 w) S: 80 mg/m^2	39	First-line Prior adjuvant chemotherapy 4	45	4.1	8.5
Inada et al. [56]	2009	P: 50 mg/m^2(w) S: 80 mg/m^2	22	First-line Prior adjuvant chemotherapy 1	55	4.7	9.5
Lee et al. [57]	2008	P: 70 mg/m^2 (w) S: 70 mg/m^2	56	First-line Prior adjuvant chemotherapy 9	40	6.6	12.1
Narahara et al. [58]	2008	P: 40 mg/m^2 (w) S: 80 mg/m^2	29	First-line 24 Second-line 5	48	NR	13.9
Ueda et al. [59]	2006	P: 50 mg/m^2 (w) S: 80 mg/m^2	54	First-line	46	6.1	14.5
Takiuchi et al. [60]	2008	P: 80 mg/m^2(w) 5'DFUR: 600 mg/m^2	35	Second-line S-1-refractory	18	4.0	10.9
Lee et al. [61]	2009	P: 75 mg/m^2 (2 w) F: 2400 mg/m^2 L: 40 mg	30	First-line Prior adjuvant chemotherapy 5	40	3.9	8.8

n, number of patients; C, cisplatin; U, UFT; F, 5-FU; L, folinic acid (LV); P, paclitaxel; S, S-1; 5'DFUR, doxifluridine; RR, response rate; NR, not reported

biweekly administration of paclitaxel plus S-1. Because the background of patients who are eligible for a combination of paclitaxel with oral agents is assumed to be better, because of their possibility of oral intake, it is not necessarily surprising that paclitaxel plus S-1 showed the most marked improvement in prognosis in patients with advanced and metastatic gastric cancer.

Paclitaxel chemotherapy for peritoneal dissemination and ascites

Peritoneal dissemination and ascites seem to be one of the most horrible and wretched features of gastric cancer. Only eight reports were found to have evaluated the effect of paclitaxel for peritoneal carcinomatosis, a common pattern of failure among gastric cancer patients. In case studies, complete disappearance of gastric ascites was reported to have been brought

about by treatment with weekly [66] and biweekly [67] paclitaxel plus either S-1 or doxifluridine [68]. Two pharmacokinetic studies demonstrated that the paclitaxel concentration in ascites remained within the optimal effective level for 72 h after intravenous administration [69, 70]. In two clinical trials, the efficacy of second-line paclitaxel or paclitaxel-containing regimens against gastric ascites was examined in patients whose disease had been refractory to fluorinated pyrimidine therapy. Monotherapy with paclitaxel resulted in the disappearance of ascites in 3 of 21 patients (14%) [71], and, in a study of combination therapy with doxifluridine, it was reported that the treatment resolved or decreased pleural effusion or ascites in 73% of the patients [72]. These two clinical trials did not primarily target gastric ascites patients, and so a new phase II clinical trial is now under way to evaluate the effect of paclitaxel specifically in patients with ascites, adopting a new concept of clinical benefit response, and an accurate and conventional five-point method for the quantitative evaluation of ascites using computed tomography [73, 74]. In addition, a new clinical trial has been started to evaluate the effect of intravenous paclitaxel and cisplatin or intraperitoneal paclitaxel administration alone [75] for preventing peritoneal carcinomatosis in patients with macroscopic peritoneal metastasis and/or peritoneal cytology-positive advanced gastric cancer.

Although peritoneal dissemination and ascites carcinomatosis was long considered to be the representative final stage of advanced gastric cancer, these new clinical trials may be able to shed some light on treatment for such disappointing situations.

Chemoradiation therapy for locally advanced gastric cancers

For advanced disease, few chemoradiation therapies using paclitaxel have been performed. Paclitaxel combined with cisplatin and radiotherapy was first reported by Safran et al. [76] in 2000. In that study, 50 mg/m^2 paclitaxel was administered weekly, five times, combined with a total dose of 45 Gy, using 1.8-Gy daily fractions. The total dose given in 5 weeks with this regimen, and the systemic effects besides radiosensitization were considered, and a safe and effective dose and schedule of paclitaxel and cisplatin were determined in this study.

Recently, a new phase I trial has been started to reevaluate the effect of combination chemoradiation therapy containing paclitaxel for gastric cancer. In this study, weekly paclitaxel 50 mg/m^2 and cisplatin 20 mg/m^2, together with radiation therapy complying with Safran's regimen and schedule, were determined as the safe and effective recommended doses [77].

Neoadjuvant and adjuvant chemoradiation therapy for curatively resected gastric cancer

Effective loco-regional treatments are also needed for curatively resected locally advanced gastric cancers. In the United States and in Europe, even when resection of all gross macroscopic disease has been done with residual cell-negative margins, the recurrence risk is not necessarily substantially reduced. In the absence of earlier diagnosis, therefore, there is a clear need to develop innovative multidisciplinary treatment strategies that will increase the potentially curative resection rate and decrease the risk of recurrence after the operation.

Macdonald et al. [78] advocated a chemoradiation regimen of 5-FU and leucovorin combined with postoperative radiation therapy of 45 Gy in an optimal adjuvant setting of macroscopically negative stomach tumor cell presence, and reported a significant benefit of chemoradiotherapy over surgery alone. With regard to paclitaxel-containing adjuvant regimens together with radiation therapy, we found studies of two such regimens; one consisted of paclitaxel plus 5-FU [79], and one of bolus paclitaxel, 5-FU, and cisplatin [80]. Both these chemoradiation regimens appear favorable, with an acceptable toxicity and prognosis. In Europe, four consecutive multicenter phase II studies of adjuvant chemoradiation trials for high-risk gastric cancer have been performed [81]. In one of these studies, irradiation with 45 Gy plus 5-FU, leucovorin, cisplatin, and paclitaxel was administered, and a median progression-free survival of 23 months was reported [81].

Concerning neoadjuvant therapy, Ajani et al. [82, 83] reported two phase II trials of preoperative paclitaxel-containing chemoradiation regimens for patients with primary gastric cancer. One regimen consisted of 5-FU and paclitaxel and concurrent radiation of 45 Gy [82], and the other of 5-FU, leucovorin, and cisplatin followed by concurrent radiation and chemotherapy (infusional 5-FU and weekly paclitaxel) [83]. The latter study, with 49 patients, resulted in a pathological complete response (CR) rate of 26% and an R0 resection rate of 77%. These results proved that for locally advanced gastric cancer, a preoperative chemoradiation strategy achieved a pathological CR rate of more than 20% in a cooperative group setting. Because the quality of surgery was improved, with 50% of the patients receiving D2 dissection, refinements of the treatment strategy for chemoradiotherapy might be poised for a randomized comparison with postoperative adjuvant chemotherapy or chemoradiotherapy in patients with gastric cancer in the Western world.

Future perspectives

The introduction of paclitaxel during the past two decades has expanded the treatment options for many types of cancer patients. This was most evident in breast, ovarian, and lung cancers.

With regard to gastric cancers, many phase I and phase II trials have been implemented and reported, suggesting the potential effect of paclitaxel either for advanced disease, or for curatively resected gastric cancers in an adjuvant setting. The principal concern is that there have been very few randomized clinical trials of paclitaxel for gastric cancers. There are still many more questions to be answered; for example, whether paclitaxel should be chosen mainly as a second-line treatment in advanced disease, and what type of combination or sequential therapy with paclitaxel and other agents is the safest and the most effective for advanced and/or metastatic cancers. In an adjuvant setting, likewise, a variety of 5-FU-based multiagent regimens plus paclitaxel may have the chance to exert better benefits than the actual standard chemoradiation therapy used in the United States, preoperative chemotherapy, surgery, postoperative-chemotherapy (CSC) therapy in the United Kingdom, or oral S-1 treatment in Japan.

Several trials are underway to determine the effect of oral fluorinated pyrimidines and paclitaxel in advanced disease, and one trial has completed entry [84]. Regarding adjuvant chemotherapy, after a feasibility study to confirm the safety of the regimen in an adjuvant setting [85], one large trial, the Stomach Cancer Adjuvant Multi-institutional Trial Group (SAMIT) trial, is currently accruing more than 1300 patients; the trial will further define the benefits of paclitaxel and oral fluorinated pyrimidines in the treatment of curatively resected gastric cancers [86]. The substitution of platinum compounds such as oxaliplatin, and the addition of molecular targeted agents such as epidermal growth factor inhibitors and vascular endothelial growth factor inhibitors are future active areas of clinical research.

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References

1. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol 2001;2:533–43.
2. Jemal A, Thomas A, Murray T, Ghafoor A, Samuels A, Ward E, et al. Cancer statistics, 2004. CA Cancer J Clin 2002;54:8–29.
3. Ajani JA. Current status of therapy for advanced gastric carcinoma. Oncology 1998;12:99–102.
4. Koizumi W, Narahara H, Hara T, Takegane A, Akira T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008;9:215–21.
5. Wani MC, Taylor HL, Wall ME. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. J Am Chem Soc 1971;93:2325–7.
6. Schiff PB, Fant J, Horbitz SB. Promotion of microtubule assembly in vivo by taxol. Nature 1979;277:665–7.
7. Crossin KL, Carney DH. Microtubule stabilization by taxol inhibits initiation of DNA synthesis by thrombin and by epidermal growth factor. Cell 1981;27:341–50.
8. Poruchynsky MS, Wang EE, Rudin CM. Bcl-xl is phosphorylated in malignant cells following microtubule disruption. Cancer Res 1998;58:3331–8.
9. Dumontet C, Sikic BI. Mechanism of action of and resistance to antibulin agents: microtubule dynamics, drug transport and cell death. J Clin Oncol 1999;17:1061–70.
10. Burkhart CA, Berman JW, Swindell CS. Relationship between the structure of taxol and other taxanes on induction of tumor necrosis factor–α gene expression and cytotoxicity. Cancer Res 1994;54:5779–82.
11. Monzo M, Rossel R, Sanchez JJ. Paclitaxel resistance in non-small cell lung cancer associated with β-tubulin gene mutations. J Clin Oncol 1999;17:1786–93.
12. Horwitz SB, Cohen D, Rao S. Taxol: mechanisms of action and resistance. J Natl Cancer Inst 1993;15:55–61.
13. Webstar L, Linsenmeyer M, Millward M. Measurement of cremophor EL following taxol: plasma levels sufficient to reverse drug exclusion mediated by the multi-drug resistant phenotype. J Natl Cancer Inst 1993;85:1685–90.
14. Oltvai ZN, Milliman CL, Korsmeyer SJ. Bcl-2 heterodimerizes in vivo with a conserved homolog, Bax, that accelerates programmed cell death. Cell 1993;74:609–19.
15. Scatena CD, Stewart ZA, Mays D. Mitotic phosphorylation of Bcl-2 during normal cell cycle progression and taxol-induced growth arrest. J Biol Chem 1998; 273;30:777–84.
16. Rowensky EK, Chaudhry V, Cornblath DR. Neurotoxicity of Taxol. J Natl Cancer Inst 1993;15:107–15.
17. Gelmon K, Eisenhauer E, Bryce C. Randomized phase II study of high dose paclitaxel with or without amifostine in patients with metastatic breast cancer. J Clin Oncol 1999;17:3038–47.
18. Hofstra LS, De Vries EG, Willemse PH. Ophthalmic toxicity following paclitaxel infusion. Ann Oncol 1997;8:1053.
19. Martoni A, Zamagni C, Gheka A, Pannuti F. Antihistamines in the treatment of taxol induced paroxystic pain syndrome. J Natl Cancer Inst 1993;85:676.
20. Rowinsky EK, McGuire WP, Guarnieri T. Cardiac disturbances during the administration of taxol. J Clin Oncol 1991;9:1704–12.
21. Cascinu S, Graziano F, Cardarelli N, Marcellini M, Giordani P, Menichetti ET, Catalano G. Phase II study of paclitaxel in pretreated advanced gastric cancer. Anticancer Drugs 1998;9:307–10.
22. Ajani JA, Fairweather J, Dumas P, Patt YZ, Pazdur R, Mansfield PF. Phase II study of Taxol in patients with advanced gastric carcinoma. Cancer J Sci Am 1998;4:269–74.
23. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, et al. Phase II trial of paclitaxel by 3-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 2001; 12:1133–7.
24. Yamaguchi K, Tada M, Horikoshi N, Otani T, Takiuchi H, Saitoh S, et al. Paclitaxel Gastric Cancer Study Group in Japan. Phase II study of paclitaxel with 3-h infusion in patients with advanced gastric cancer. Gastric Cancer 2002;5:90–5.

25. Vanhoefer U, Harstrick A, Wilke H et al. Schedule-dependent antagonism of paclitaxel and cisplatin in human gastric and ovarian carcinoma cell lines in vitro. Eur J Cancer 1995; 31A:92–7.
26. Bokemeyer C, Hartmann JT, Lampe CS, Clemens MR, Quietzsch D, Forkmann L, Kanz L. Paclitaxel and weekly 24-hour infusion of 5-fluorouracil/folinic acid in advanced gastric cancer. Semin Oncol. 1997;24 (6 Suppl 19):S19–100
27. Murad AM, Petroianu A, Guimaraes RC et al. Phase II trial of the combination of paclitaxel and 5-fluorouracil in the treatment of advanced gastric cancer: a novel, safe, and effective regimen. Am J Clin Oncol 1999;22:580–6.
28. Kim YH, Shin SW, Kim BS et al. Paclitaxel, 5-fluorouracil, and cisplatin combination chemotherapy for the treatment of advanced gastric carcinoma. Cancer 1999;85:295–301.
29. Kollmannsberger C, Quietzsch D, Haag C et al. A phase II study of paclitaxel, weekly, 24-hour continuous infusion 5-fluorouracil, folinic acid, and cisplatin in patients with advanced gastric cancer. Br J Cancer 2000;83:458–62.
30. Stathopoulos GP, Rigatos SK, Fountzilas G, Polyzos A, Stathopoulos JG. Paclitaxel and carboplatin in pretreated advanced gastric cancer: a phase II study. Oncol Rep 2002;9: 89–92.
31. Gadgeel SM, Shields AF, Heilbrun LK et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. Am J Clin Oncol 2003; 26: 37–41.
32. Park SR, Oh DY, Kim DW, Kim TY, Heo DS, Bang YJ, et al. A multi-center, late phase II clinical trial of Genexol (paclitaxel) and cisplatin for patients with advanced gastric cancer. Oncol Rep 2004;12:1059–64.
33. Chang HM, Kim TW, Ryu BY, Choi SJ, Park YH, Lee JS, et al. Phase II study of paclitaxel and carboplatin in advanced gastric cancer previously treated with 5-fluorouracil and platinum. Jpn J Clin Oncol 2005;35:251–5.
34. Shin SJ, Chun SH, Kim KO, Kim MK, Lee KH, Hyun MS, et al. The efficacy of paclitaxel and cisplatin combination chemotherapy for the treatment of metastatic or recurrent gastric cancer: a multicenter phase II study. Korean J Intern Med 2005;20: 135–40.
35. Lee KW, Im SA, Yun T, Song EK, Na I, Shin H, et al. Phase II trial of low-dose paclitaxel and cisplatin in patients with advanced gastric cancer. Jpn J Clin Oncol 2005;35:720–6.
36. Park SH, Lee WK, Chung M, Lee Y, Han SH, Bang SM, et al. Paclitaxel versus docetaxel for advanced gastric cancer: a randomized phase II trial in combination with infusional 5-fluorouracil. Anticancer Drugs 2006;17:225–9.
37. Lee KW, Kim JH, Yun T, Song EK, Na II, Shin H, et al. Phase II study of low-dose paclitaxel and cisplatin as a second-line therapy after 5-fluorouracil/platinum chemotherapy in gastric cancer. J Korean Med Sci 2007;22 (Suppl):S115–21.
38. Im CK, Jeung HC, Rha SY, Yoo NC, Noh SH, Roh JK, Chung HC. A phase II study of paclitaxel combined with infusional 5-fluorouracil and low-dose leucovorin for advanced gastric cancer. Cancer Chemother Pharmacol 2008;61:315–21.
39. Kang HJ, Chang HM, Kim TW, Ryu MH, Sohn HJ, Yook JH, et al. A phase II study of paclitaxel and capecitabine as first-line combination chemotherapy for advanced gastric cancer. Br J Cancer 2008;98:316–22.
40. Hwang J, Cho SH, Shim HJ, Lee SR, Ahn JS, Yang DH, et al. Phase II study of paclitaxel, cisplatin, and 5-fluorouracil combination chemotherapy in patients with advanced gastric cancer. J Korean Med Sci 2008;23:586–91.
41. Jung JY, Kwon JH, Kim JH, Song HH, Kim I, Lee KS, et al. Phase II study of the paclitaxel, cisplatin, 5-fluorouracil and leucovorin (TPFL) regimen in the treatment of advanced or metastatic gastric cancer. Oncol Rep 2009;21:523–9.
42. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol. 2008;26:1585–7.
43. Kodera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, et al. Chubu Clinical Cancer Group. A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). Anticancer Res 2007;27: 2667–71.
44. Emi Y, Yamamoto M, Takahashi I, Orita H, Kakeji Y, Kohnoe S, Maehara Y. Phase II study of weekly paclitaxel by 1-hour infusion for advanced gastric cancer. Surg Today 2008;38: 1013–20.
45. Honecker F, Kollmannsberger C, Quietzsch D, Haag C, Schroeder M, Spott C, et al. Phase II study of weekly paclitaxel plus 24-h continuous infusion 5-fluorouracil, folinic acid and 3-weekly cisplatin for the treatment of patients with advanced gastric cancer. Anticancer Drugs 2002;13:497–503.
46. Yeh KH, Lu YS, Hsu CH, Lin JF, Hsu C, Kuo SH, et al. Phase II study of weekly paclitaxel and 24-hour infusion of high-dose 5-fluorouracil and leucovorin in the treatment of recurrent or metastatic gastric cancer. Oncology 2005;69:88–95.
47. Mochiki E, Ohno T, Kamiyama Y, Aihara R, Haga N, Ojima H, et al. North Kanto Gastric Cancer Study Group. Phase I/II study of S-1 combined with paclitaxel in patients with unresectable and/or recurrent advanced gastric cancer. Br J Cancer 2006;95: 1642–7.
48. Chao Y, Li CP, Chao TY, Su WC, Hsieh RK, Wu MF, et al. An open, multi-centre, phase II clinical trial to evaluate the efficacy and safety of paclitaxel, UFT, and leucovorin in patients with advanced gastric cancer. Br J Cancer 2006;95:159–63.
49. Kawabata R, Fujiwara Y, Doki Y, Fujita J, Tsukahara Y, Yamasaki M, et al. Phase I/II study of a combination of S-1 and weekly paclitaxel in patients with advanced or recurrent gastric cancer. Oncology 2007;72:219–25.
50. Ninomiya M, Kondo K, Matsuo K, Hirabayashi N, Kojima H, Kobayashi M, et al. Japanese South West Oncology Group (JASWOG). Multicenter phase II trial of combination chemotherapy with weekly paclitaxel and 5-fluorouracil for the treatment of advanced or recurrent gastric carcinoma. J Chemother 2007;19:444–50.
51. Kim YH, Yamaguchi K, Bang YJ, Takiuchi H, Kang WK, Sato A, et al. Phase II study of biweekly paclitaxel and cisplatin combination chemotherapy in advanced gastric cancer: Korea Japan Collaborative Study Group Trial. Jpn J Clin Oncol 2007;37: 501–8.
52. Kim JG, Sohn SK, Song HS, Kwon KY, Do YR, Lee KH, et al. Multicenter phase II study of weekly paclitaxel plus cisplatin combination chemotherapy in patients with advanced gastric cancer. Cancer Chemother Pharmacol 2007;60:863–9.
53. Gu Y, Shu Y, Xu Q. A study of weekly paclitaxel plus 5-fluorouracil and cisplatin for patients with advanced or recurrent inoperable gastric cancer. Biomed Pharmacother 2009;63:293–6.
54. Nagata N, Kimura M, Hirabayashi N, Tuburaya A, Murata T, Kondo K, et al. Phase II study of weekly paclitaxel and cisplatin combination therapy for advanced or recurrent gastric cancer. Hepatogastroenterology 2008;55:1846–50.
55. Nakajo A, Hokita S, Ishigami S, Miyazono F, Etoh T, Hamanoue M, et al. Kyushu Taxol TS-1 Study Group. A multicenter phase II study of biweekly paclitaxel and S-1 combination chemotherapy for unresectable or recurrent gastric cancer. Cancer Chemother Pharmacol 2008;62:1103–9.
56. Inada S, Tomidokoro T, Fukunari H, Sato T, Hatano T, Nishimura A, et al. Phase I/II trial of combination therapy with S-1 and weekly paclitaxel in patients with unresectable or recurrent gastric cancer. Cancer Chemother Pharmacol 2009;63:267–73.
57. Lee JJ, Kim SY, Chung HC, Lee KH, Song HS, Kang WK, et al. A multi-center phase II study of S-1 plus paclitaxel as first-line

therapy for patients with advanced or recurrent unresectable gastric cancer. Cancer Chemother Pharmacol 2009;63:1083–90.
58. Narahara H, Fujitani K, Takiuchi H, Sugimoto N, Inoue K, Uedo N, et al. Phase II study of a combination of S-1 and paclitaxel in patients with unresectable or metastatic gastric cancer. Oncology 2008;74:37–41.
59. Ueda Y, Yamagishi H, Ichikawa D, Morii J, Kakihara N, Yamashita T, et al. Kyoto Gastrointestinal Cancer Chemotherapy Group. Phase II study of a combination of S-1 and weekly paclitaxel in patients with advanced or recurrent gastric cancer. Proc ASCO 2006;24:No. 18S.
60. Takiuchi H, Goto M, Imamura H, Furukawa H, Imano M, Imamoto H, et al. Multi-center phase II study for combination therapy with paclitaxel/doxifluridine to treat advanced/recurrent gastric cancer showing resistance to S-1 (OGSG 0302). Jpn J Clin Oncol 2008;38:176–81.
61. Lee HJ, Chodo Y, Park JC, Bae SB, Lee KT, Cho IS, et al. Phase II trial of biweekly paclitaxel plus infusional 5-fluorouracil and leucovorin in patients with advanced or recurrent inoperable gastric cancer. Cancer Chemother Pharmacol 2009;63:427–32.
62. Kondo K, Kobayashi M, Kojima H, Hirabayashi N, Kataoka M, Araki K, et al. Phase I evaluation of continuous 5-fluorouracil infusion followed by weekly paclitaxel in patients with advanced or recurrent gastric cancer. Jpn J Clin Oncol 2005;35:332–7.
63. Nagata N, Kobayashi M, Kojima H, Kondo K, Hirabayashi N, Matsui T, et al. Phase I study of paclitaxel and cisplatin for patients with advanced or recurrent gastric cancer. Hepatogastroenterology 2005;52:1905–10.
64. Hara T, Omura K, Hirano M, Asada Y, Munemoto Y, Sakamoto J. A phase I study of paclitaxel, cisplatin, and fluorouracil (TCF) for advanced gastric cancer. Cancer Chemother Pharmacol 2007;59:631–6.
65. Ueda Y, Yamagishi H, Ichikawa D, Morii J, Koizumi K, Kakihara N, et al. Phase I study of a combination of S-1 and weekly paclitaxel in patients with advanced or recurrent gastric cancer. Oncology 2005;69:261–8.
66. Koizumi Y, Obata H, Hara A, Nishimura T, Sakamoto K, Fujiyama Y. A case of scirrhous gastric cancer with peritonitis carcinomatosa controlled by TS-1 + paclitaxel for 36 months after diagnosis. World J Gastroenterol 2007;13:470–3.
67. Nakajo A, Natsugoe S, Hokita S, Ishigami S, Takatori H, Arigami T, et al. Successful treatment of advanced gastric cancer by surgical resection following combination chemotherapy with oral S-1 and biweekly paclitaxel. Gastric Cancer 2007;10:58–62.
68. Takeyoshi I, Iwanami K, Yamada T, Kawate S, Hamada K, Sunose Y, et al. Advanced gastric cancer with peritoneal dissemination successfully treated with paclitaxel and doxifluridine: a case report. Hepatogastroenterology 2005;52:322–5.
69. Kobayashi M, Sakamoto J, Namikawa T, Okamoto K, Okabayashi T, Ichikawa K, Araki K. Pharmacokinetic study of paclitaxel in malignant ascites from advanced gastric cancer patients. World J Gastroenterol 2006;12:1412–5.
70. Kobayashi M, Oba K, Sakamoto J, Kondo K, Nagata N, Okabayashi T, et al. Pharmacokinetic study of weekly administration dose of paclitaxel in patients with advanced or recurrent gastric cancer in Japan. Gastric Cancer 2007;10:52–7.
71. Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006;9:14–8.
72. Arai W, Hosoya Y, Hyodo M, Haruta H, Kurashina K, Saito S, et al. Doxifluridine combined with weekly paclitaxel for second-line treatment in patients with gastric cancer resistant to TS-1. Int J Clin Oncol 2007;12:146–9.
73. Sakamoto J, Morita S, Yumiba T, Narahara H, Kinoshita K, Nakane Y, et al.; Ascitic Gastric Cancer Study Group of the Japan South West Oncology Group. A phase II clinical trial to evaluate the effect of paclitaxel in patients with ascites caused by advanced or recurrent gastric carcinoma: a new concept of clinical benefit response for non-measurable type of gastric cancer. Jpn J Clin Oncol 2003;33:238–40.
74. Oriuchi N, Nakajima T, Mochiki E, Takeyoshi I, Kanuma T, Endo K, Sakamoto J. A new, accurate and conventional five-point method for quantitative evaluation of ascites using plain computed tomography in cancer patients. Jpn J Clin Oncol 2005; 35:386–90.
75. Kodera Y, Ito Y, Ito S, Ohashi N, Mochizuki Y, Yamamura Y, et al. Intraperitoneal paclitaxel: a possible impact of regional delivery for prevention of peritoneal carcinomatosis in patients with gastric carcinoma. Hepatogastroenterology. 2007;54:960–3.
76. Safran H, Wanebe HJ, Hesketh PJ, Akerman P, Iannitti, D. Cioffi W. Paclitaxel and concurrent radiation for gastric cancer. Int Radiat Oncol Biol Phys 2000;46:889–94.
77. Yoshikawa T, Tsuburaya A, Hirabayashi N, Yoshida K, Nagata N, Kodera Y, et al. A phase I study of palliative chemoradiation therapy with paclitaxel and cisplatin for local symptoms due to an unresectable primary advanced or locally recurrent gastric adenocarcinoma. Cancer Chemother Pharmacol 2009. doi: 10.1007/s00280-009-0963-3.
78. Macdonald JS, Smally SR, Beneditti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach of gastrointestinal junction. N Engl J Med 2001;345:725–30.
79. Constantinou M, Tsai JY, Safran H. Paclitaxel and concurrent radiation in upper gastrointestinal cancers. Cancer Invest 2003; 21:887–96.
80. Kollmannsberger C, Budach W, Stahl M, Schieucher N, Hehr T, Wilke H, et al. Adjuvant chemoradiation using 5- fluorouracil / folinic acid/cisplatin with or without paclitaxel and radiation in patients with completely resected high-risk gastric cancer: two comparative phase II studies of the AIO/ARO/ACO. Ann Oncol 2005;16:1326–33.
81. Oechsle K, Bokemeyer C, Hartmann JT, Budach W, Trarbach T, Stahl M. et al. Four consecutive multicenter phase II trials of adjuvant chemoradiation in patients with completely resected high-risk gastric cancer: the experience of the German AIO/ ARO/CAO group. J Cancer Res Clin Oncol 2009;135:163–72.
82. Ajani JA, Mansfield PF, Crane CH, Wu TT, Lunagomez S, Lynch PM. Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. J Clin Oncol 2005;23:1237–44.
83. Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. J Clin Oncol 2006;24:3953–8.
84. Morita S, Baba H, Tsuburaya A, Takiuchi H, Matsui T, Maehara Y, Sakamoto J. A randomized phase II selection trial in patients with advanced/recurrent gastric cancer: Trial for Advanced Stomach Cancer (TASC). Jpn J Clin Oncol 2007;37:469–72.
85. Kobayashi M, Tsuburaya A, Nagata N, Miyashita Y, Oba K, Sakamoto J. A feasibility study of sequential paclitaxel and S-1 (PTX/S-1) chemotherapy as postoperative adjuvant chemotherapy for advanced gastric cancer. Gastric Cancer 2006;9:114–9.
86. Tsuburaya A, Sakamoto J, Morita S, Kodera Y, Kobayashi M, Miyashita Y, Macdonald JS. A randomized phase III trial of postoperative adjuvant oral fluoropyrimidine versus sequential paclitaxel/oral fluoropyrimidine; and UFT versus S1 for T3/T4 gastric carcinoma: the Stomach Cancer Adjuvant Multi-institutional Trial Group (SAMIT) Trial. Jpn J Clin Oncol 2005 Nov;35: 672–5.

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Individual Patient Based Meta-analysis of Lentinan for Unresectable/Recurrent Gastric Cancer

KOJI OBA[1], MICHIYA KOBAYASHI[2], TAKANORI MATSUI[3], YASUHIRO KODERA[4] and JUNICHI SAKAMOTO[5]

[1]EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto;
[2]Department of Human Health and Medical Sciences, Kochi Medical School, Kochi;
[3]Department of Clinical Research, Aichi Cancer Center Prefectural Aichi Hospital, Okazaki;
[4]Department of Surgery II and [5]Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

Abstract. *Background: In the present study, the effect of immunochemotherapy with lentinan compared with that of chemotherapy alone was evaluated in patients with advanced gastric cancer through individual patient data (IPD) meta-analysis. Materials and Methods: Based on a computerized and manual search, all eligible centrally randomized controlled trials (RCT) which compared chemotherapy regimens with or without lentinan administration for advanced gastric cancer patients were included. Results: In total, 650 IPD from 5 trials were available. Lentinan significantly prolonged the overall survival (stratified log-rank p=0.011). The overall hazard ratio (HR) was 0.80 (95% confidence interval=0.68-0.95) and there was no heterogeneity between trials. Additionally, lentinan was possibly more effective in patients with lymph-node metastasis than in non-node metastasis patients (P for interaction=0.077). Conclusion: The addition of lentinan to standard chemotherapy offers a significant advantage over chemotherapy alone in terms of survival for patients with advanced gastric cancer.*

The per annum incidence and mortality of gastric cancer are estimated at about 930,000 and 700,000 gastric cancer patients in the world (1). Although both incidence and mortality have decreased in developed countries, it ranks as the second most common cause of cancer mortality worldwide and remains a significant problem in global health terms. In particular, advanced/recurrent gastric cancer, especially that deemed to be inoperable, remains an incurable disease. Several drugs and combinations of chemotherapy have been investigated, but response rates and 5-year survival rates of patients have not been markedly improved (2-5).

Biological response modifiers (BRMs) are widely used with cytotoxic agents for gastric cancer therapy. BRMs stimulate the immune system to reject and destroy tumors and such immunochemotherapy is expected to exert a synergistic effect. In adjuvant settings, the benefit of immuno-chemotherapy using polysaccharide K (PSK) has been shown in one randomized clinical trial and through meta-analysis involving 8,009 patients from eight randomized controlled trials (RCT) (6, 7). Similarly, Sakamoto *et al.* conducted a meta-analysis involving 1,522 patients from six clinical trials of immunochemotherapy with penicillin-killed lyophilized *Streptococcus pyogenes* (OK-432) and suggested that OK-432 may improve the survival of patients with curatively resected gastric cancer (8). However, the beneficial effects for patients with advanced/recurrent gastric cancer are still unclear. Popiela *et al.* explored the survival prolonging effect of *Bacillus Calmette-Guérin* (BCG) and 5-fluorourinated pyrimidine (5-FU) compared with 5-FU alone or surgery alone over 20 years ago, but there was no significant difference in patients with non-resectable tumors after 2-year follow-up (9).

Lentinan, which is a purified polysaccharide isolated from *Lentinus edodes*, has been shown to have some antitumor activity (10, 11). In Japan, lentinan is clinically administered to patients with unresectable advanced gastric cancer, and post-operative gastric cancer patients with recurrent disease, usually in combination with tegafur (T). However, there is insufficient evidence from large RCTs to recommend immunochemotherapy with lentinan in patients with unresectable/recurrent gastric cancer. In the present study, an individual patient data (IPD) meta-analysis was conducted with the aim of evaluating the effect of immunochemotherapy with lentinan compared with that of chemotherapy alone for patients with advanced unresectable/recurrent gastric cancer.

Correspondence to: Koji Oba, M.S., EBM Research Center, Kyoto University Graduate School of Medicine, Yoshidakonoe-cho, Sakyo-ku, Kyoto, Japan 606-8501. Tel: +81 757521519, Fax: +81 757521532, e-mail: oba@pbh.med.kyoto-u.ac.jp

Key Words: Lentinan, meta-analysis, advanced gastric cancer, clinical trials.

Materials and Methods

Search strategy. A computerized and manual search of the electronic databases Medline and PubMed and the Japanese Ichu-shi was performed to identify all RCT of Lentinan used for unresectable/recurrent gastric cancer patients. The same search strategy for RCT of unresectable/recurrent gastric cancer as the Cochrane Review (4), which is a combination of medical subject headings (MeSH) and text words, was used, and additionally used the MeSH and text words related to the use of immunochemotherapy with lentinan were included. Review papers were also examined for published results. Duplication of data was avoided by examining the body of each publication or the names of all the authors. To ensure that all relevant studies were included, enquiries were made of the researchers with area expertise about the possible existence of unpublished trials. The following eligibility criteria for the target trials were used. i) The study was aimed at the evaluation of the survival effect of chemotherapy regimen with or without lentinan administration for advanced unresectable or recurrent gastric cancer patients. ii) It was a central RCT (including trials using envelope methods). iii) A control arm received the same chemotherapy as the therapeutic arm. iv) The trial was concluded before the end of 2007. After the identification of eligible trials, the collaboration of the relevant investigators in this meta-analysis and the provision of the latest version of the IPD were requested.

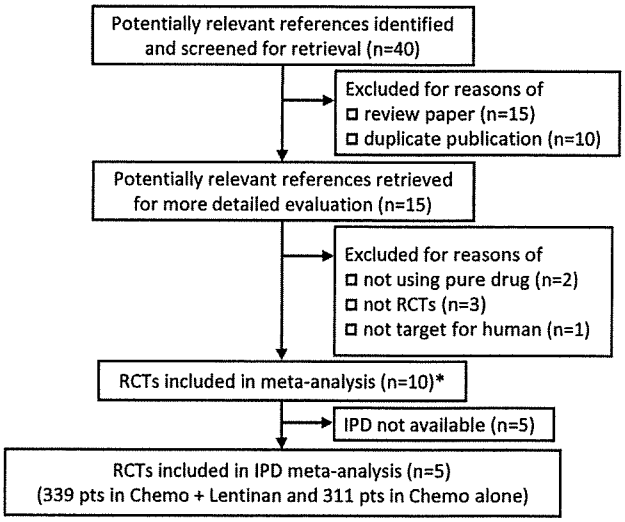

Figure 1. *Flow diagram through the stages of the meta-analysis. *One reference (25) included 2 trials. RCT, Randomized controlled trial; IPD, individual patient data. pts, patients.*

Statistical analysis. The primary analysis included all the available IPD of the eligible trials. Overall survival was analyzed through a stratified two-sided log-rank test, with trial as the stratification factor. In addition, the hazard ratio (HR) and 95% confidence interval (CI) were calculated as the measure for assessing the survival benefits of lentinan from Cox's proportional hazard model stratified by trials. If data on important prognostic factors were available, multiple Cox's proportional hazard model was used to check whether the estimates of treatment effects changed after adjustment for these factors. A forest plot of the HRs was produced for overall survival. Subgroup analyses were also performed according to meaningful patient characteristics, with an interaction test to assess the statistical significance of any observed differences between the treatment effects in different subgroups.

A HR of less than 1.0 indicates a beneficial effect of immunochemotherapy and a ratio equal to or more than 1.0 is thought to demonstrate a harmful effect. The analysis was based on the intention-to-treat principle and defined a statistical test result with a two-sided p-value less than 0.05 was defined as significant. SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) was used for all the analyses.

Results

Trial screening. Figure 1 shows the flow diagram through the stages of the meta-analysis. In total, forty references were identified as potentially relevant to the study (8 references from Medline and PubMed, 31 references from Japanese database (Ichu-shi), and one reference from handsearching of review papers and queries from the researchers with area expertise). After excluding review references as well as duplicate publications, 15 potential relevant references remained for further evaluation (12-26).

Two trials out of 15 references were excluded because functional food containing superfine lentinan and not the pure drug was used (12, 13). In addition, three trials were not RCTs (14, 15, 23) and one trial evaluated the effect of lentinan on mice (25). After detailed evaluation, nine references met the eligibility criteria. Since Taguchi evaluated two RCTs using different regimens (T plus lentinan or not, and 5-FU+mitomycin plus lentinan or not) in one reference (24), they were considered as different trials. In the potentially eligible 10 RCTs, 650 IPD (68.2%) were acquired out of 953 patients' data from five trials (19, 20, 24, 26) and IPD were not obtained from five trials because the data were discarded (16-18, 21, 22). The five trials from which IPD were received were labeled as the Chiba study (19), the Hokkaido study (20), the FT study (24), the MF study (24), and the Tohoku study (26).

Trial and patient characteristics. Table I shows the eligible trial and patient characteristics for the IPD meta-analysis. All the trials used regimens based on the combination of fluorinated pyrimidines and Lentinan. The FT, MF and Tohoku studies were conducted in the early 80's and the others were in the late 80's. There was little difference about the baseline characteristics between the studies, but the Hokkaido study mostly enrolled non-recurrent patients and surgery was conducted in all the patients in the study. In addition, patients did not undergo surgery in the Tohoku study. For all the available IPD, the proportion of hepatic metastasis in the chemotherapy plus Lentinan group was smaller than the chemotherapy alone group (34.5% *vs.* 43.1%), but the other factors balanced well between the two groups.

Treatment effect of lentinan on the overall survival. Two hundred and eighty patients (82.6%) and 262 patients (84.2%) died during 6.0 months of median follow-up in the

Table I. *Trial and patient characteristics for the IPD meta-analysis.*

	All available IPD		Chiba study		Hokkaido study		FT study		MF study		Tohoku study	
	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone
N	339	311	45	44	24	25	111	104	105	85	54	53
Regimen	-	-	MMC *i.v.* 4 mg, UFT oral 400 mg/day (or T *i.v.* 800 mg/day), lentinan *i.v.* 2 mg/week	MMC, UFT (or T)	MMC *i.v.* 0.25 mg/kg, UFT oral 300 mg/day, lentinan *i.v.* 2 mg/week	MMC, UFT	T *i.v.* 600 mg/day, lentinan *i.v.* 2 mg/week	T	MMC *i.v.* 12 mg/m^2, 5FU *i.v.* 250 mg/day lentinan *i.v.* 2 mg/week	MMC, 5FU	MMC *i.v.* 12 mg/m^2, 5FU *i.v.* 250 mg/day lentinan *i.v.* 2 mg/week	MMC, 5FU
Trial start	-	-	Feb 1987		May 1987		Aug 1979		Aug 1979		Oct 1980	
Trial end			May 1989		Apr 1989		May 1984		May 1984		Mar 1983	
Age	61.3 (SD=12.1)	61.1 (SD=12.3)	60.4 (SD=9.5)	63 (SD=10.5)	62.6 (SD=12.6)	63.8 (SD=9.7)	61.7 (SD=12.6)	61.6 (SD=12.9)	60.5 (SD=12.6)	59.0 (SD=13.1)	62.1 (SD=12.0)	60.9 (SD=11.8)
Gender, female	112 (33.0%)	92 (29.6%)	12 (26.7%)	15 (34.1%)	8 (33.3%)	7 (28.0%)	38 (34.2%)	26 (25.0%)	40 (38.1%)	24 (28.2%)	14 (25.9%)	20 (37.7%)
PS, ≥2	251 (74.7%)	216 (70.8%)	23 (50.1%)	19 (44.2%)	10 (41.7%)	8 (32.0%)	86 (77.4%)	78 (75.7%)	87 (83.7%)	70 (83.3%)	41 (82.0%)	44 (86.5%)
Recurrent	102 (30.2%)	93 (30.0%)	11 (24.4%)	12 (27.3%)	1 (4.7%)	2 (8.0%)	35 (31.5%)	30 (28.9%)	33 (31.4%)	33 (38.8%)	22 (41.5%)	16 (30.8%)
Prior therapy	138 (41.1%)	124 (40.0%)	17 (39.5%)	17 (38.6%)	0 (0.0%)	0 (0.0%)	56 (50.5%)	46 (44.2%)	40 (38.1%)	37 (43.5%)	25 (47.2%)	24 (46.2%)
Surgery	122 (36.1%)	106 (34.2%)	15 (33.3%)	7 (15.9%)	24 (100.0%)	25 (100.0%)	43 (38.7%)	35 (33.7%)	31 (29.5%)	28 (32.9%)	9 (17.0%)	11 (21.2%)
Peritoneal metastasis	50 (14.9%)	40 (12.9%)	17 (37.8%)	16 (36.4%)	13 (54.2%)	12 (48.0%)	10 (9.1%)	5 (4.8%)	10 (9.6%)	4 (4.7%)	0 (0.0%)	3 (5.7%)
Hepatic metastasis	116 (34.5%)	134 (43.1%)	10 (22.2%)	12 (27.3%)	9 (37.5%)	7 (28.0%)	34 (30.9%)	47 (45.2%)	39 (37.5%)	46 (54.1%)	24 (45.3%)	22 (41.5%)
Lymph node metastasis	129 (38.5%)	136 (44.0%)	12 (26.7%)	10 (22.7%)	22 (95.7%)	22 (95.7%)	45 (40.9%)	45 (43.3%)	35 (33.7%)	36 (42.4%)	15 (28.3%)	23 (43.4%)

IPD, Individual patient data; MMC, mitomycin C; UFT, tegafur-uracil; T, tegafur; 5-FU, 5-fluorinated pyrimidine; SD, standard deviation. *i.v.*, intravenous injection; PS, performance status.

chemotherapy plus lentinan and the chemotherapy alone groups, respectively. The Kaplan-Meier curve is depicted in Figure 2. The median survival time (MST) was 139 days in the chemotherapy plus lentinan group and 114 days in the chemotherapy alone group. The combination of chemotherapy based on mainly fluorinated pyrimidines and lentinan statistically significantly prolonged the overall survival (stratified log-rank p-value=0.011). The overall HR was 0.80 (95% CI=0.68-0.95) and there was no heterogeneity between trials (heterogeneity p-value=0.466, Figure 3). The HR adjusted by trial and nine baseline characteristics (age, sex, performance status (≥2 or not), recurrent, prior therapy, surgery, peritoneal metastasis, hepatic metastasis, lymph-node metastasis) was 0.76 (95% CI=0.64-0.90; p=0.002).

Table II shows the baseline characteristics and the results in each reference whose IPD were not available. Most of the trials were conducted in the late '80s. The baseline characteristics were slightly different between the eligible trials with available IPD and those without available IPD, but the MST of the immunochemotherapy group also seemed to be longer than that of the chemotherapy group in the latter trials. This trend for the beneficial effect of lentinan was the same as the primary results based on the IPD meta-analysis.

Subgroup analysis was conducted based on six baseline characteristics (age less than 65 or not, gender, recurrent or inoperable advanced gastric cancer, peritoneal metastasis, hepatic metastasis, lymph node metastasis). Figure 4 shows the HRs and corresponding 95% CI. There was no significant interaction, but the immunochemotherapy was probably more effective in the patients with lymph node metastasis than in those without (p-value for interaction=0.077).

Some hematological and nonhematological adverse events were reported in the two treatment regimens (19 leucopenia (5.6%), 32 thrombocytopenia (9.4%), 13 anorexia (3.8%) and 6 nausea (1.8%) in the immunochemotherapy with lentinan; 5 leucopenia (1.6%), 45 thrombocytopenia

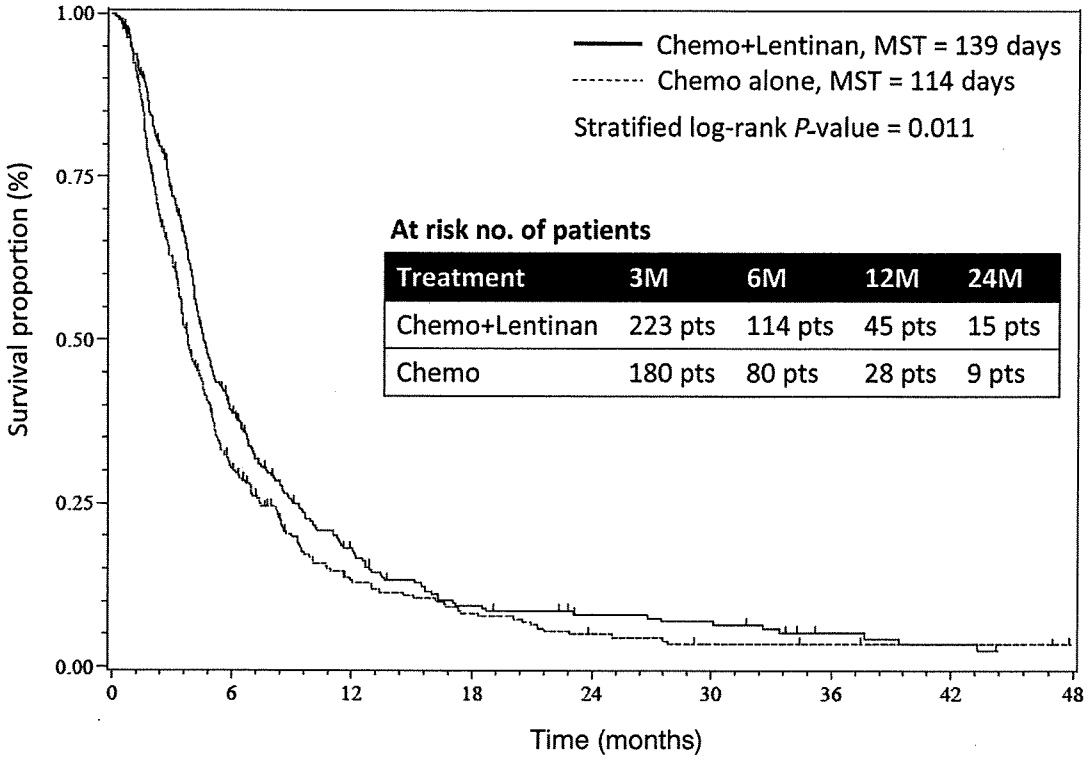

Figure 2. *Kaplan-Meier curve of overall survival. MST, median survival time.*

(14.5%), 13 anorexia (4.2%) and 6 nausea (1.9%) in the chemotherapy alone), but none of them were severe and all were reversible and manageable.

Discussion

Out of the ten RCTs conducted to date, the FT and MF studies were relatively large, but most were of small sample size and those could not conclude whether the immunochemotherapy with lentinan in comparison with chemotherapy alone was beneficial or not. The present IPD meta-analysis of the 650 patients' data showed that the combination immunotherapy of fluorinated pyrimidines and lentinan had a modest, but significant overall survival benefit for patients with advanced, unresectable or recurrent gastric cancer. Since IPD meta-analysis provides one of the highest levels of evidence, this result is meaningful for the future treatment development for advanced gastric cancer.

Recently, two phase III trials of S-1, which is composed of T, gimestat and otastat potassium in a molar ratio of 1:0.4:1, in patients with advanced gastric cancer have been reported from Japan. In JCOG 9912, the combination of irinotecan and cisplatin was not better than 5-FU alone, but S-1 was no worse than 5-FU (MST of the S-1 arm was reported as 11.4 months) (27). The SPIRIT trial showed that the MST of S-1 plus cisplatin (13·0 months) was significantly longer than that of S-1 alone (11·0 months) (28). In response to these results, S-1 or the combination of S-1 and cisplatin seem to be the standard treatment for advanced gastric cancer especially in Eastern countries. If S-1 becomes a standard treatment in the advanced setting, it would be interesting to confirm the synergistic effect of lentinan with S-1. Nimura *et al.* reported a preliminary result that the MST for the immunochemotherapy combination with S-1 and lentinan reached 559 days for 32 unresected/recurrent advanced gastric cancer patients in a phase II study (14). Oka *et al.* are conducting a phase III trial to investigate the superiority of a combination of S-1 and lentinan compared to S-1 alone in advanced or recurrent gastric cancer in (29) and this is the focus of considerable interest.

The present meta-analysis also showed that immunochemotherapy with lentinan may be especially effective in patients with lymph node metastasis. The immunesuppressed status of patients with advanced cancer has been reported (30). It is still unclear, but BRMs such as lentinan or PSK are considered to alter the immunological background and activate cytotoxic effector cells or helper cells in patients with far advanced cancer (31). The antitumor immune reactivity is especially suppressed in patients with lymph node metastasis, which might link to the present results of that subgroup.

Some limitations of the present IPD meta-analysis must be mentioned. First, while over two-thirds of IPD were collected for this meta-analysis, 303 patients' data

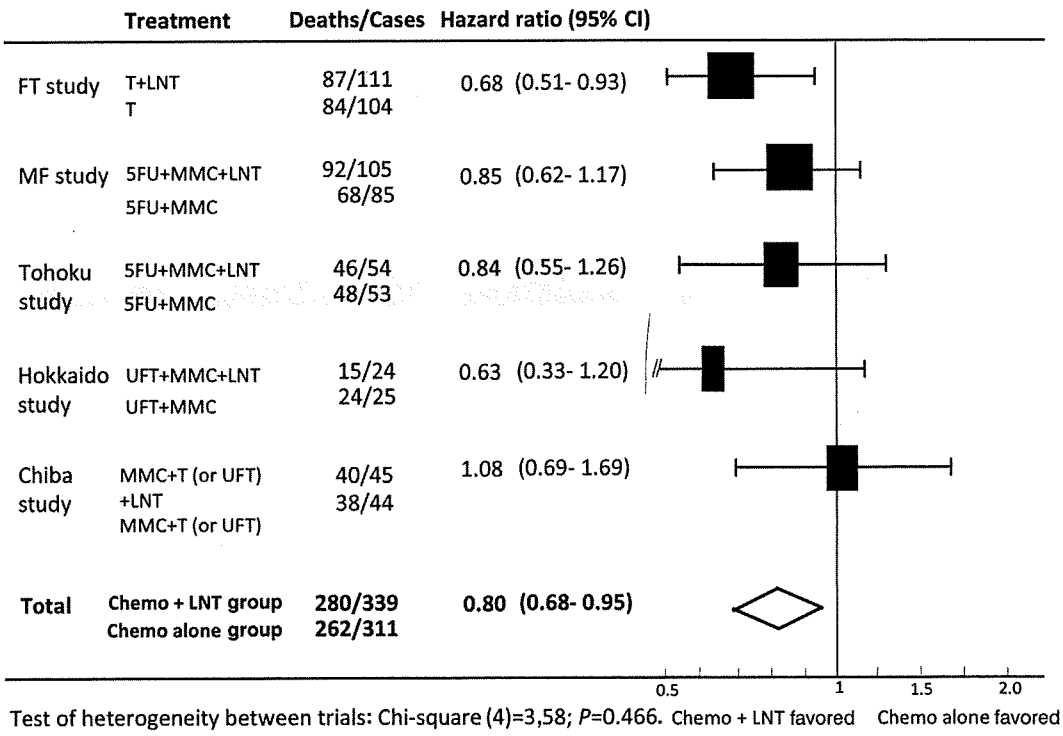

Figure 3. *Forest plot of hazard ratios and corresponding 95% confidence intervals. LNT, Lentinan; MMC, mitomycin C; T, tegafur; 5-FU, 5-fluorinated pyrimidine; UFT, tegafur-uracil.*

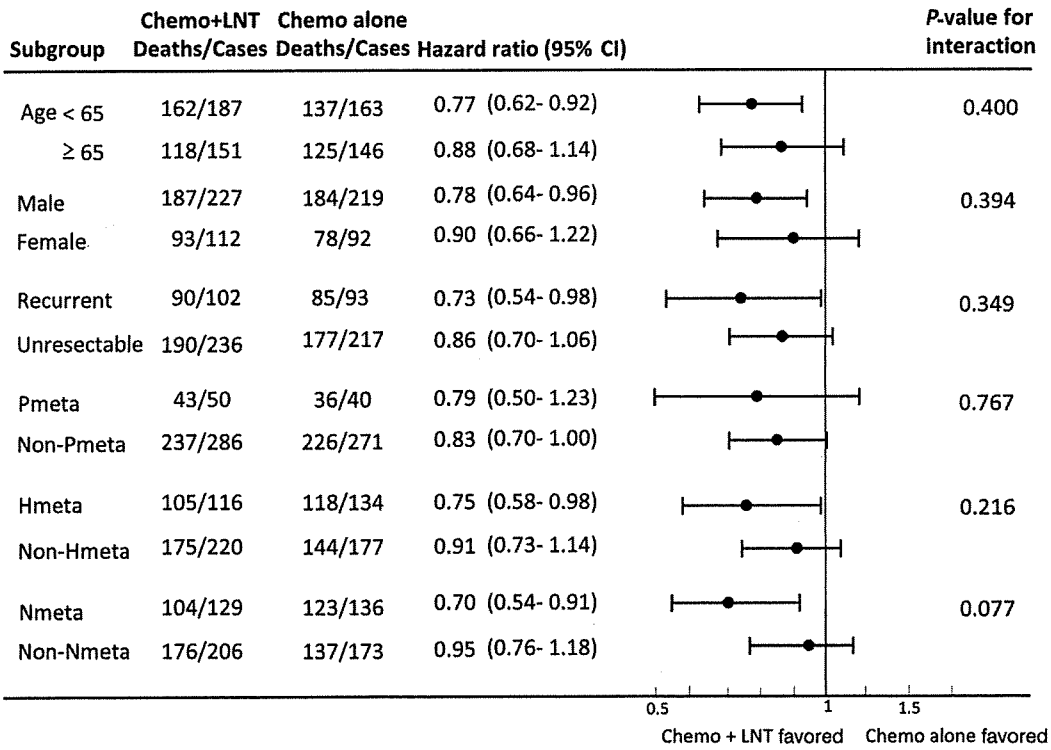

Figure 4. *Subgroup analysis based on 6 baseline characteristics. LNT, Lentinan; MMC, mitomycin C; T, tegafur; 5-FU, 5-fluorinated pyrimidine; Pmeta, peritoneal metastasis; Hmeta, hepatic metastasis; Nmeta, lymph-node metastasis.*

Table II. *Patient characteristics and results in each reference whose IPD were not available.*

	Nakano *et al.* (16)		Tanemura *et al.* (17)		Wakui *et al.* (18)		Iwase *et al.* (21)		Kameta *et al.* (22)*	
	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone	Chemo+ lentinan	Chemo alone
N	23	22	59	49	20	22	20	20	23/14	18/13
Regimen	T oral 600 mg/ day CDDP *i.v.* 20 mg/m^2 lentinan *i.v.* 2 mg/body/day	T CDDP	T oral 600 mg/ day (or 5-FU) MMC *i.v.* 10 mg/body ADM *i.v.* 30-50 mg lentinan *i.v.* 2 mg/week	T (or 5-FU) MMC ADM	T oral 800 mg/day Lentinan *i.v.* 2 mg/week	T	UFT oral 400 mg/m^2/day MMC *i.v.* 4 mg/m^2/week lentinan 2 mg/week	UFT MMC	FU (or 5-FU+ MTX) lentinan	FU (or 5-FU+ MTX)
Trial start	Nov 1993		1986		Mar 1987		Apr 1988		Nov 1986	
Trial end	Sep 1995		1996		Jun 1991		Oct 1989		Apr 1988	
Age, Mean	62.9	65.8	(21-80)†	(31-80)†	<80†	<80†	61	59	n.s.†	n.s.†
Gender, female	7 (30.4%)	4 (18.2%)	18 (30.5%)	17 (34.7%)	9 (45.0%)	7 (31.8%)	9 (45.0%)	7 (35.0%)	10 (43.5%) /5 (35.7%)	4 (22.2%) /10 (76.9%)
PS, ≥2	-	-	33 (55.9%)	23 (50.0%)	10 (50.0%)	12 (54.5%)	4 (20.0%)	7 (35.0%)	16 (69.6%) /13 (92.9%)	13 (72.2%) /13 (100%)
Recurrent	6 (26.0%)	4 (18.2%)	28 (47.5%)	25 (51.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-
Prior therapy	-	-	-	-	20 (100.0%)	22 (100.0%)	20 (100.0%)	20 (100.0%)	13 (56.5%) /0 (0.0%)	16 (88.9%) /13 (92.9%)
Peritoneal metastasis	10 (43.5%)	10 (45.5%)	26 (63.4%)	27 (64.3%)			-	-	-	-
Hepatic metastasis	2 (8.7%)	5 (22.7%)	11 (25.6%)	6 (15%)	19 (95.0%)	20 (90.9%)	14 (70.0%)	9 (45.0%)	11 (47.8%) /3 (21.4%)	4 (22.2%) /1 (7.7%)
Lymph node metastasis	5 (21.7%)	5 (22.7%)	36 (94.7%)	38 (100.0%)			10 (50.0%)	9 (45.0%)	-	-
MST (days)	297	199	209	121	116	117	214	189	154/247	97/157
HR (95% CI)	-	-	-	-						
p-Value	0.028		0.0045		0.105		n.s.		<0.05/n.s.	

IPD, Individual patient data; MMC, mitomycin C; T, tegafur; 5-FU, 5-fluorinated pyrimidine; CDDP, cisplatin; *i.v.*, intravenous injection; PS, performance status; ADM, adriamicin; FU, fluorinated pyrimidines; MTX, methotrexate; MST, median survival time; HR, hazard ratio; *Kameta *et al.* (22) reported the results of inoperable advanced/recurrent separately, but dose, schedule, and route of administration were not reported. †Mean age was not reported.

unfortunately could not be retrieved because the data were discarded. It is possible that collected data were biased. However, the results shown in the papers of the uncollected data did not differ from the present primary results, which means that the uncollected data would not have changed the conclusion. Second, the randomization methods were most envelope methods. The envelope randomization methods have generally proven to be somewhat problematic in several respects. The major problem is that participating physicians may have sometimes violated and interfered with the randomization process, especially in the studies started during the early 1980s. However, the important prognostic factors were adjusted using the multiple Cox proportional hazard model. The adjusted HR was 0.76 (95% CI=0.64-0.90; p=0.002) and this was consistent with the primary result. IPD meta-analysis could possibly minimize the bias caused by envelope methods. Finally, the proportion of hepatic metastasis in the chemotherapy plus lentinan group was smaller than in the chemotherapy alone group (34.5% *vs.* 43.1%). However, the result was not changed after adjustment using the multiple Cox regression analysis, thus it was considered that this difference between treatment groups did not influence the conclusion.

In conclusion, the addition of lentinan to standard chemotherapy offers a significant advantage over chemotherapy alone in terms of survival for patients with advanced, unresected/recurrent gastric cancer. It is hoped these results will result in wider acceptance of immunochemotherapy for the treatment of advanced gastric cancer.

References

1 GLOBOCAN database in International Agency for Research on Cancer. Available *via* http://www-dep.iarc.fr/ accessed February 04, 2009.

2 Sastre J, García-Saenz JA and Díaz-Rubio E: Chemotherapy for gastric cancer. World J Gastroenterol *12*: 204-213, 2006.

3 Berardi R, Scartozzi M, Romagnoli E, Antognoli S and Cascinu S: Gastric cancer treatment: a systematic review. Oncol Rep *11*: 911-916, 2004.
4 Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A and Fleig WE: Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol *24*: 2903-2909, 2006.
5 Wohrer SS, Raderer M and Hejna M: Palliative chemotherapy for advanced gastric cancer. Ann Oncol *15*: 1585-1595, 2004.
6 Nakazato H, Koike A, Saji S, Ogawa N and Sakamoto J: Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. Study Group of Immunochemotherapy with PSK for Gastric Cancer. Lancet *343*: 1122-1126, 1994.
7 Oba K, Teramukai S, Kobayashi M, Matsui T, Kodera Y and Sakamoto J: Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curative resections of gastric cancer. Cancer Immunol Immunother *56*: 905-911, 2007.
8 Sakamoto J, Teramukai S, Nakazato H, Sato Y, Uchino J, Taguchi T *et al*: Efficacy of adjuvant immunochemotherapy with OK-432 for patients with curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials. J Immunother *25*: 405-412, 2002.
9 Popiela T, Zembala M, Oszacki J and Jedrychowski W: A follow-up study on chemoimmunotherapy (5-fluorouracil and BCG) in advanced gastric cancer. Cancer Immunol Immunother *13*: 182-184, 1982.
10 Chihara G, Hamuro J, Maeda Y, Arai Y and Fukuoka F: Fractionation and purification of the polysaccharides with marked antitumor activity, especially lentinan, from *Lentinus edodes* (an edible mashroom). Cancer Res *30*: 2776-2781, 1970.
11 Maeda Y and Chihara G: The effects of neonatal thymectomy on the antitumor activity of lentinan, carboxymethylpachymaran and zymosan. and their effects on various immune responses. Int J Cancer *11*: 153-161, 1973.
12 Yoshino S, Watanabe H, Imano M, Yagi M, Suga T and Nakazawa S: Evaluation of efficacy for immune adjuvant (Lentinan (β-1, 3-glucan))-containing supplementary food in patients with unresectable and recurrent gastric cancer. Biotherapy *21*: 265-273, 2007.
13 Odagiri Y, Masuyama T, Ohishi K, Suga T and Yasuda K: Safety trial for functional food containing superfine dispersed lentinan(β-1, 3-glucan) – trial of repetitive dosing ingestion in healthy adult volunteer –. Biotherapy *20*: 578-589, 2006.
14 Nimura H, Mitsumori N, Takahashi N, Kashimura H, Takayama S, Kashiwagi H *et al*: S-1 combined with lentinan in patients with unresectable or recurrent gastric cancer. Jpn J Cancer Chemother *33*: 106-109, 2006.
15 Kimura Y, Iijima S, Kato T, Tujie M, Naoi Y, Hayashi T *et al*: Usefulness of TS-1 and lentinan combination immuno-chemotherapy in advanced or recurrent gastric cancer – pilot study aiming at a randomized trial. Jpn J Cancer Chemother *30*: 1125-1130, 2003.
16 Nakano H, Namatame K, Nemoto H, Motohashi H, Nishiyama K and Kumada K, for the Kanagawa lentinan research group: A multi-institutional prospective study of lentinan in advanced gastric cancer patients with unresectable and recurrent disease: effect on prolongation of survival and improvement of quality of life. Hepatogastroenterology *46*: 2662-2668, 1999.
17 Tanemura H, Saji S, Miya K, Tanaka S, Misawa K, Tsuchiya J *et al*: Clinical controlled study on significance of immuno-chemotherapy with lentinan for advanced or recurrent gastric cancer (final report). Biotherapy *10*: 60-65, 1996.
18 Wakui A, Urushizaki I, Furue H, Taguchi T and Ogawa N: A randomized trial of tegafur alone *versus* tegafur plus lentinan in inoperable schirrhous gastric cancer. Biotherapy *7*: 1224-1233, 1993.
19 Ochiai T, Isono K, Suzuki T, Koide Y, Gunji Y, Nagata M *et al*: Effect of immunotherapy with lentinan on patients' survival and immunological parameters in patients with advanced gastric cancer: results of a multi-centre randomized controlled study. Int J Immunother *8*: 161-169, 1992.
20 Ebata T, Totsuka M, Uchino J, Kondo Y, Tanabe T, Katoh H *et al*: Clinical effects of lentinan on advanced gastric cancer – randomized controlled study. Biotherapy *5*: 721-733, 1991.
21 Iwase H, Morise K, Kusugami K Inagaki T, Horiuchi Y, Ina K *et al*: A randomized controlled trial of UFT-mitomycin (UFT-M) chemotherapy and UFT-M plus lentinan therapy for advanced gastric cancer. Oncologia *24*: 74-80, 1991.
22 Kameta C, Akazawa S, Miyoshi K, Tamiya M, Kondo Y, Kurosawa T *et al*: A clinical randomized controlled trial of lentinan. Biotherapy *4*: 941-948, 1990.
23 Nishihara T, Akimoto M and Mori S: Anti-cancer effects of BRMs associated with nutrition in cancer patients. Jpn J Cancer Chemother *15*: 1615-1620, 1988.
24 Taguchi T: Clinical efficacy of lentinan on patients with stomach cancer: end point results of a four-year follow-up survey. Cancer Detect Prev Suppl *1*: 333-349, 1987.
25 Akimoto M, Nishihira T and Kasai M: Modulation of antitumor effect of BRM under various nutritional or endocrine conditions. Jpn J Cancer Chemother *13*: 1270-1276, 1986.
26 Wakui A, Kasai M, Konno K, Abe R, Kanamaru R, Takahashi K *et al*: Randomized study of lentinan on patients with advanced gastric and colorectal cancer –Tohoku lentinan study group–. Jpn J Cance Chemother *13*: 1050-1059, 1986.
27 Boku N, Yamamoto S, Shirao K, Doi T, Sawaki A, Koizumi W *et al*: Randomized phase III study of 5-fluorouracil (5-FU) alone *versus* combination of irinotecan and cisplatin (CP) *versus* S-1 alone in advanced gastric cancer. (JCOG9912). Proc Am Soc Clin Oncol (abstr); p.LBA4513, 2007.
28 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M *et al*: S-1 plus cisplatin *versus* S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol *9*: 215-221, 2008.
29 Oka M, for the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC): The information of randomized phase III study of TS-1 alone *versus* TS-1 plus lentinan in advanced or recurrent gastric cancer (JFMC36-0701) registered in the UMIN Clinical Trials Registry (UMIN-CTR). Available *via* https:// center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000000696&type=summary&language=E) accessed February 04, 2009.
30 Shibata M, Nezu T, Fujisaki S, Andou K, Tomita R and Fukuzawa M: Clinical potential of biological response modifiers combined with chemotherapy for gastric cancer. Dig Surg *19*: 255-260, 2002.
31 Sugiyama Y, Saji S and Ishihara K. Clinical and immunological evaluation of immunochemotherapy using low dose 5-FU/cisplatin and lentinan. Biotherapy *11*: 1238-1244, 1997.

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