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Review article

Paclitaxel chemotherapy for the treatment of gastric cancer

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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.

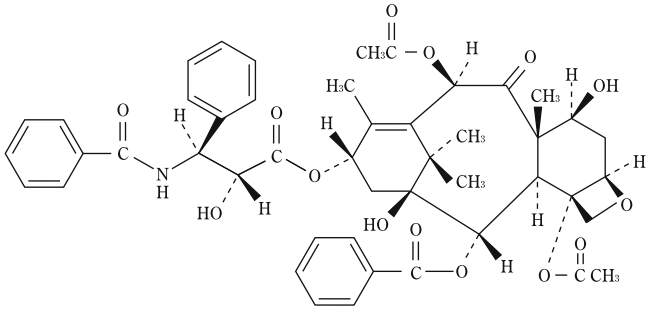

Fig. 1. The chemical structure of paclitaxel

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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