Review article

Docetaxel: its role in current and future treatments for advanced gastric cancer

MASAHIKO NISHIYAMA^{1,2} and SATORU WADA^{1,2}

¹Translational Research Center, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan

²Project Research Division, Research Center for Genomic Medicine, Saitama Medical University, Hidaka, Japan

Abstract

A globally accepted standard chemotherapy remains undetermined in gastric cancer, but the recent introduction of active “new-generation agents” such as taxanes, irinotecan (CPT-11), oxaliplatin, S-1, and capecitabine, offers hope for markedly improving patient outcomes. Docetaxel, as well as the other new-generation agents, plays a key role in the development of the new-era chemotherapy, and the incorporation of taxanes has provided several regimens, such as docetaxel/cisplatin/5-fluorouracil (5-FU) (DCF), that could become standard treatment. The DCF regimen is now regarded as a standard treatment option in advanced gastric cancer in selected patients in good condition. Many institutions and cooperative groups continue to study a variety of docetaxel-based combinations with “new-generation cytotoxic agents” in various treatment settings, and recent attention has been focused on the incorporation of biological agents, such as cetuximab, bevacizumab, everolimus, and sunitinib, into docetaxel-containing combinations as another innovative approach. The ongoing clinical trials of a number of new regimens will clarify their clinical benefits in gastric cancer treatment. Along with the development of more active docetaxel combination regimens, the identification of predictive biomarkers for each regimen has been intensively studied recently. This review focuses on docetaxel as a key agent in gastric cancer chemotherapy, and discusses the role of this taxane in current and future treatments for advanced gastric cancer.

Key words Docetaxel · Gastric cancer · Chemotherapy

Introduction

In gastric cancer, a series of trials have produced evidence that chemotherapy increases survival, but a globally accepted standard chemotherapy and the optimal

regimen are undetermined [1–4]. Both CF (cisplatin [CDDP]/5-fluorouracil [5-FU]) and ECF (epirubicin/CDDP/5-FU) have been considered as reference regimens to date [5–8], but the median survival time (MST) of the regimens does not exceed 7–10 months.

Recently, several active agents have been used in gastric cancer therapy: the taxanes, irinotecan (CPT-11), oxaliplatin, S-1, and capecitabine, and more recently, biological agents such as cetuximab and bevacizumab have been used [1–8]. Current studies have thus focused on “new-generation agents,” and much effort has been directed towards the development of the best regimen in various treatment settings. A series of these trials have provided several regimens that could become a standard treatment: the regimens include docetaxel/CDDP/5-FU (DCF) and CDDP/S-1 for advanced and metastatic cancer, and S-1 monotherapy in the adjuvant setting [9–11]. The advent of these new-generation agents offers hope for improving patient outcomes.

Among the new-generation agents, docetaxel now appears to be one of the most extensively investigated [12]. Docetaxel has demonstrated promising activity in gastric cancer, both as monotherapy [13, 14] and in combination with other agents [15–17]. To date, docetaxel combinations, especially the DCF regimen, seem to be pivotal [9, 10], and further, a taxane has been suggested to be the best potential partner of new oral 5-FU analogues and prodrugs such as S-1 and capecitabine [16, 17]. This review will focus on the taxane, docetaxel, as a key agent in gastric cancer chemotherapy.

Docetaxel as a single agent

Mechanisms of action and metabolism

Docetaxel is a semisynthetic analogue of paclitaxel, an extract from the rare Pacific yew tree *Taxus brevifolia* [18]. The chemical structure of docetaxel differs from

that of paclitaxel at two positions, a tert-butyl carbamate ester on the phenylpropionate side chain and a hydroxyl functional group on carbon 10, which causes docetaxel to be more water-soluble than paclitaxel. Docetaxel, a second-generation taxane, binds to and stabilizes tubulin, which prevents physiological microtubule depolymerization/disassembly and results in cell-cycle arrest at the G2/M phase and cell death [19, 20]. This agent also is known to inhibit the anti-apoptotic gene *Bcl2* and to encourage the expression of *p27*, a cell-cycle inhibitor, and further pro-angiogenic factors such as vascular endothelial growth factor (VEGF) [21]. Docetaxel is mainly metabolized in the liver by the cytochrome P450 CYP3A4 and CYP3A5 subfamilies of isoenzymes [18, 22], and its clearance has been shown to be related to body surface area and hepatic enzyme and alpha1 acid glycoprotein plasma levels [23].

Clinical activity and toxicity

A series of phase II trials have shown that docetaxel monotherapy has appreciable activity in gastric cancer. Administration of docetaxel was commonly repeated every 3 weeks at a dose of 60–100 mg/m², and the overall response rate (ORR) in the front-line setting was 17%–24%, while in the second-line setting the ORR was 4.8%–22% [12, 13, 24–28]. In chemotherapy-naïve patients, docetaxel monotherapy has achieved ORRs of 18%, 20%, and 24% when given at 100 mg/m², and 18% when used at the slightly lower dose of 75 mg/m² [13, 25, 27, 28]. In the salvage setting, docetaxel single-agent therapy achieved an RR of 20% when given at 100 mg/m², and 22% when used at the dose of 60 mg/m² [29, 30].

The most common adverse reactions are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia [12, 31]. Reversible bone marrow suppression was the major dose-limiting toxicity in patients with various tumor types receiving docetaxel monotherapy at 100 mg/m² [32]; the incidence of neutropenia was 95.5%; anemia, 90.4%; febrile neutropenia, 11.0%; and thrombocytopenia, 8.0% [31]. At least 95% of these patients, however, recovered without receiving hematopoietic support. In the 40 phase II and phase III studies, deaths due to toxicity accounted for 1.7% of the 2045 patients and the incidence of such deaths was increased (9.8%) in patients with elevated baseline liver function test results (liver dysfunction).

Docetaxel-containing combinations

The early studies of docetaxel monotherapy indicated that docetaxel was well tolerated, active in advanced gastric cancer, and deserved further investigation in multidrug combination programs.

Combinations with “classical” cytotoxic drugs

For advanced, metastatic, and recurrent gastric cancer, 5-FU- and/or CDDP-based combinations are still the mainstay of treatment [1–8, 33–44] (Table 1). Both CF (CDDP/5-FU) and ECF have been recognized as the most active treatment options in various countries, especially in the United States and Europe. The MST, however, does not exceed 7–10 months with these “classical” combinations. On the basis of the encouraging results observed in monotherapy, combinations of docetaxel with the “classical” regimens or drugs have been intensively investigated. These studies have developed several active regimens including a pivotal triplet regimen, DCF (docetaxel/CDDP/5-FU), which has been approved as a treatment for advanced gastric and gastroesophageal adenocarcinoma by the Food and Drug Administration of the United States based on the results of the V-325 study group.

The V-325 study group first investigated the DCF triplet regimen (docetaxel [75 mg/m²], CDDP [75 mg/m²], and 5-FU [750 mg/m²/day × 5 days] every 3 weeks) and a doublet regimen (docetaxel [85 mg/m²] and CDDP [75 mg/m²] every 3 weeks) in a randomized phase II study [45]. This trial demonstrated that the triplet regimen (*n* = 79) was superior to the doublet one (*n* = 76) in terms of ORR (43% vs 26%), and time to progression (TTP; 5.9 months vs 5.0 months) in patients with metastatic gastric cancer. DCF was chosen as the investigational regimen based on the higher ORR and acceptable toxicity profile. The following multinational phase III trial with the endpoint of TTP enrolled and randomized 455 patients across 72 centers and 16 countries with DCF (*n* = 221) and CF (*n* = 224). The trial demonstrated that the DCF triplet regimen was superior to CF in terms of ORR (37% vs 25%; 95% confidence interval [CI], 30.3–43.4 vs 19.9–31.7; χ^2 ; *P* = 0.0106), TTP (5.6 months vs 3.7 months; hazard ratio [HR], 1.47; 95% CI, 1.19–1.82; risk reduction 32%; log-rank *P* = 0.0004), and overall survival [OS] (9.2 months vs 8.6 months; risk reduction 23%; HR, 1.29; 95% CI, 1.0–1.6; log-rank *P* = 0.0201) in patients with metastatic gastric cancer [9, 10]. The 1-year survival rates of DCF and CF were 40% and 32%, respectively, and the 2-year survival rate was doubled with the DCF regimen as compared to CF (18% vs 9%). However, DCF was more toxic than DC – grade III/IV neutropenia (82% vs 57%), leucopenia (65% vs 31%), febrile neutrope-

Table 1. Chemotherapeutic options and supporting published data (phase III study) in advanced gastric cancer

Regimen	No. of patients	ORR (%)	MST (months)	Reference
FAMTX	105	41	10.5	Wils et al. 1991 [34]
FAM	103	9	7.3	
EAP	30	20	6.1	
FAMTX	30	33	7.3	Kelsen et al. 1992 [35]
FP	103	51	9.2	
FAM	98	25	7.3	
5-FU	94	26	7.7	Kim et al. 1993 [36]
FAMTX	130	21	5.7	
ECF	126	45	8.9	
FAMTX	133	12	6.7	Webb et al. 1997 [37]
ELF	132	9	7.2	
FP	134	20	7.2	
MCF	285	44	8.7	Vanhoefer et al. 2000 [38]
ECF	289	42	9.4	
FAMTX	98	23	6.9	
PELF	97	51	7.7	Ross et al. 2002 [39]
DCF	221	37	9.2	
CF	224	25	8.6	
FLO	112	34	10.7	Cocconi et al. 2003 [40]
FLP	106	25	8.8	
ECF	263	41	9.9	
ECX	250	46	9.0	Van Cutsem et al. 2006 [9], Ajani 2007 [10]
EOF	245	42	9.3	
EOX	144	48	11.2	
S-1	234	28	11.4	Al-Batran et al. 2008 [41]
5-FU	234	9	12.3	
IC	236	38	10.8	
CS	148	54	13.0	Cunningham et al. 2008 [42]
S-1	150	31	11.4	
XP	139	41	10.5	
FP	137	29	9.3	Boku et al. 2008.[43]

ORR, overall response rate; MST, median overall survival time; FAMTX, 5-FU, doxorubicin, high-dose methotrexate; FAM, 5-FU, doxorubicin, mitomycin; EAP, etoposide, doxorubicin, CDDP; FP, 5-FU, CDDP; 5-FU, 5-FU monotherapy; ECF, epirubicin, CDDP, 5-FU; ELF, etoposide, leucovorin, 5-FU; FLP, 5-FU, leucovorin, CDDP; FLO, 5-FU, leucovorin, oxaliplatin; FP, infusional 5-FU, CDDP; PELF, CDDP, epirubicin, leucovorin, 5-FU; MCF, mitomycin, CDDP, 5-FU; DCF, docetaxel, CDDP, 5-FU days 1–5 continuous infusion; CF, CDDP, 5-FU days 1–5 continuous infusion; ECX, epirubicin, CDDP, capecitabine; EOF, epirubicin, oxaliplatin, 5-FU; EOX, epirubicin, oxaliplatin, capecitabine; S-1, S-1 monotherapy; IC, CPT-11, CDDP; CS, CDDP, S-1; XP, capecitabine, CDDP

nia/neutropenic infection (63% vs 27%), diarrhea (19% vs 8%) and neuropathy (17% vs 6%).

The two docetaxel-based regimens, DCF and DC, were evaluated and compared with ECF in a randomized phase II trial [46]. In that study, chemotherapy-naïve patients with unresectable and/or metastatic gastric cancer received ECF (epirubicin 50 mg/m² on day 1, CDDP 60 mg/m² on day 1, and 5-FU 200 mg/m² per day on days 1–21), DC (docetaxel initially 85 mg/m² on day 1; later reduced to 75 mg/m² as a result of toxicity, and CDDP 75 mg/m² on day 1), or mDCF (DC plus 5-FU 300 mg/m² per day on days 1–14). Among 119 evaluable patients, ORR was 25% for ECF, 18.5% for DC, and 36.6% for DCF. mDCF was superior to ECF and/or DC also in terms of median TTP (4.6, 4.9, and 3.6 months, respectively), and OS (10.4, 11.0, and 8.3 months), even though the initial dose of docetaxel of 85 mg/m² was reduced to 75 mg/m² due to a high rate of febrile neutropenia in the mDCF and DC arms, and grade III/IV neutropenia occurred in more treatment

cycles with docetaxel (DC, 49%; mDCF, 57%; ECF, 34%). A trend was observed towards increased myelosuppression and infectious complications with mDCF vs DC or ECF. mDCF was more active than ECF, but more toxic. A considerably higher rate of complicated neutropenia and substantially improved quality of life (QOL) with the DCF regimen suggested proper patient selection and management for DCF.

Although the increased toxicity of DCF was controllable and was suggested not to negatively affect QOL or clinical benefit, the regimen was highly toxic. Optimizing studies of the original regimen, in terms of both efficacy and safety, are now ongoing [4, 12, 47] (Table 2). Indeed, in the above-mentioned phase II trials by Roth et al. [46], the dose reduction of docetaxel from 85 to 75 mg/m² decreased febrile neutropenia for both docetaxel-containing regimens (mDCF, 28%–12%; DC, 15%–4%) without significant decrease of the activity. In a phase II trial performed by Lorenzen et al. [48], which treated patients with docetaxel (50 mg/m²) and

CDDP (50 mg/m^2) on days 1, 15, and 29, and 5-FU (2000 mg/m^2) and leucovorin (400 mg/m^2) weekly, in 8-weekly cycles, secondary dose reduction of both docetaxel and CDDP to 40 mg/m^2 was required to decrease the rates of grade III or IV neutropenia, febrile neutropenia, and thrombocytopenia. The T-PLF (docetaxel/CDDP/leucovorin/FU) phase II study provided an ORR of 47%, TTP of 9.4 months, and OS of 17.9 months. Park et al. [49] developed an mDCF regimen with a lower dose of docetaxel (50 mg/m^2) than the regimen of Lorenzen et al. [48]. In the Park et al. [49] regimen, docetaxel was given on day 1 in combination with CDDP (80 mg/m^2) and 5-FU (1200 mg/m^2 , days 1–3), and repeated every 3 weeks. The ORR in 47 chemotherapy-naïve patients with metastatic gastric cancer was 40%, while TTP was 4.6 months and OS was 9.7 months. Rates of grade III or IV neutropenia (68%) and febrile neutropenia/neutropenic infection (26%) were less common than those in previously reported high-dose DCF regimens.

Combinations with “new-generation agents”

DCF was proven to be active, but substantial toxicity was observed, which prompted investigators to explore alternative docetaxel-containing regimens for gastric cancer (Table 2). Much attention has been focused on new-generation agents as putative partners of docetaxel.

Combinations with new oral fluoropyrimidines. A docetaxel/fluoropyrimidine combination is a very potent modality for gastric cancer treatment. In a phase II study in patients with advanced gastric cancer without prior chemotherapy, docetaxel combined with a continuous infusion of 5-FU (DF) showed potent efficacy compared with ECF; among patients treated with DF and ECF, respectively, the ORRs were 37.8% and 35.6%, median TTPs were 5.5 and 5.3 months, and median survivals were 9.5 and 9.7 months [15]. Even so, the response of DF is still limited. Instead of 5-FU, new oral 5-FU analogues and prodrugs such as S-1 and capecitabine are becoming key agents in gastric cancer chemotherapy. These agents are very attractive alternative agents for combination with docetaxel [16, 17].

Recent phase III trials have focused on the use of oral 5-FU, especially with S-1, and have demonstrated pivotal activities: a three arm phase III study (Japan Clinical Oncology Group [JCOG] 9912) showed that S-1 monotherapy seemed to be superior to 5-FU and comparable with a CPT-11/CDDP combination, in that there was a significantly lower incidence of grade 3, 4 toxicity than that seen with CPT-11/CDDP [43]. A S-1 plus cisplatin vs S-1 alone for the first line treatment of advanced gastric cancer (SPIRITS) trial, comparing S-1

monotherapy with an S-1/CDDP combination, further demonstrated that the S-1/CDDP combination significantly improved OS (11 vs 13 months; $P = 0.0366$), and progression-free survival (PFS; 4 vs 6 months; $P < 0.0001$) at a median follow up of 34.6 months [11]. On the basis of these findings, treatment with combined S-1 plus CDDP has become a standard treatment option in Japan. Capecitabine has also been shown to be effective in the treatment of advanced esophagogastric cancer in a phase III study comparing capecitabine with fluorouracil in combination with epirubicin/oxaliplatin or epirubicin/CDDP [42]. The randomized ECF for locally advanced esophago-gastric cancer-2 (REAL-2) trial, comparing ECF, EOF (epirubicin/oxaliplatin/5-FU), ECX (epirubicin/CDDP/capecitabine), and EOX (epirubicin/oxaliplatin/capecitabine) showed that the efficacy of capecitabine was equivalent to that of 5-FU, and that EOX significantly improved survival time compared with ECF. An MST of 11.2 months in the EOX regimen was among the longest achieved in this patient setting. Although both of these trials (i.e., the trial carried out by Cunningham et al. [42] and the REAL-2 trial) were designed to assess whether capecitabine was no worse than 5-FU, the findings generally suggested better outcome in patients who received oral capecitabine.

In addition to the observed clinical benefit of S-1 and capecitabine, in an experimental model, Wada et al. [50] suggested that docetaxel could enhance fluoropyrimidine activity through the modification of the intracellular metabolic enzymes—thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), and orotate phosphoribosyl transferase (OPRT)—which are related to fluoropyrimidine resistance, the actions of these agents thereby being synergistically cytotoxic in human gastrointestinal cancer cells. New oral fluoropyrimidines might be the best partners of docetaxel.

Indeed, a combination of docetaxel and S-1 (docetaxel 40 mg/m^2 day 1 and oral S-1 80 mg/m^2 per day on days 1–14 every 3 weeks) was shown to be highly active in advanced and recurrent gastric cancer, and had an acceptable and manageable toxicity profile in a phase II study [16]. The combination achieved promising results for OR rate (56.2%; 95% CI, 38%–66%), median TTP (7.3 months; 95% CI, 4.3–10.0 months), and median OS (14.3 months; 95% CI, 10.7–20.3 months). Nonhematologic toxicities were generally mild and none was greater than grade 3. Stomatitis, the most common grade 3 nonhematologic toxicity, was observed in just 8.3% of patients. The predominant toxicity was myelosuppression, and grade 3–4 neutropenia occurred in 58.3% of patients. However, both the hematologic and nonhematologic toxicities were generally manageable and, in most cases, treatment could be continued in the outpatient setting. The results reported are consistent with

Table 2. Docetaxel combinations with cytotoxic agents and supporting published data (phase II studies) in advanced gastric cancer

Regimen	Dose and schedule	No. of patients	ORR (%)	MST (months)	Reference
Triplet and quartet regimens					
mDCF	Docetaxel 50 mg/m ² and cisplatin 80 mg/m ² on day 1, 5-FU, 1200 mg/m ² per day on days 1–3 (3-weekly cycle)	47	40	9.7	Park et al. 2005 [49]
mDCF	Docetaxel 85→75 mg/m ² and cisplatin 75 mg/m ² on day 1, 5-FU 300 mg/m ² per day on days 1–14 (3-weekly cycle)	61	37	10.4	Roth et al. 2007 (randomized phase II trial) [46]
DC	Docetaxel 85→75 mg/m ² and cisplatin 75 mg/m ² on day 1 (3-weekly cycle)	58	18	8.3	
ECF	Epirubicin 50 mg/m ² and cisplatin 60 mg/m ² on day 1, 5-FU 200 mg/m ² per day on days 1–21 (3-weekly cycle)	59	25	11.0	
mDCF (T-PLF)	Docetaxel 50→40 mg/m ² and cisplatin 50→40 mg/m ² on days 1, 15, 29, 5-FU 2000 mg/m ² /leucovorin 400 mg/m ² (8-weekly cycle)	60	47	17.9	Lorenzen et al. 2007 [48]
FLOT	Oxaliplatin 85 mg/m ² , leucovorin 200 mg/m ² , and fluorouracil 2600 mg/m ² as a 24-h infusion in combination with docetaxel 50 mg/m ² on day 1 (2-weekly cycle)	59	51	11.3	Al-Batran et al. 2008 [59]
EDOCOX	Epirubicin 50 mg/m ² , docetaxel 60 mg/m ² followed by oxaliplatin 100 mg/m ² on day 1 (3-weekly cycle)	40	48	12.1	Di Lauro et al. 2009 [58]
TPC	Docetaxel 30 mg/m ² , cisplatin 25 mg/m ² , and irinotecan 65→50 mg/m ² (3-weekly cycle)	56	54	11.9	Enzinger et al. 2009 [63]
Doublet regimens					
DI	Irinotecan 160→120 mg/m ² followed by docetaxel 65→50 mg/m ² (3-weekly cycle)	132	20	8.9	Sym et al. 2008 [62]
	Docetaxel 30 mg/m ² and irinotecan 70 mg/m ² on days 1 and 8 (3-weekly cycle)	46	46	8.2	Park et al. 2006 [61]
DC	Docetaxel 85 mg/m ² and cisplatin 75 mg/m ² on day 1 (3-weekly cycle)	76	26	10.5	Ajani et al. 2005 (randomized phase II trial) [45]
DCF	Docetaxel 75 mg/m ² , cisplatin 75 mg/m ² on day 1, and fluorouracil 750 mg/m ² per day as continuous infusion on days 1–5 (3-weekly cycle)	79	43	9.6	
DF	Docetaxel 75 mg/m ² day 1, and fluorouracil 200 mg/m ² days 1–21 (3-weekly cycle)	45	38	9.5	Thuss-Patience et al. 2005 (randomized phase II trial) [15]
ECF	Epirubicin 50 mg/m ² day 1, cisplatin 60 mg/m ² day 1, and fluorouracil 200 mg/m ² days 1–21 (3-weekly cycle)	45	36	9.7	
DX	Docetaxel 36 mg/m ² on days 1 and 8, and capecitabine 1000 mg/m ² twice a day on days 1–14 (3-weekly cycle)	47	40	12.0	Chun et al. 2005 [17]
DS	Docetaxel 40 mg/m ² day 1 and oral S-1 80 mg/m ² per day on days 1–14 (3-weekly cycle)	48	56	14.3	Yoshida et al. 2006 [16]
		46	46	14.0	Yamaguchi et al. 2006 [51]
DOCOX	Docetaxel 60 mg/m ² followed by oxaliplatin 130 mg/m ² on day 1 (3-weekly cycle)	71	36	8.5	Richards et al. 2008 [55]
	Docetaxel 65 mg/m ² and oxaliplatin 120 mg/m ² on day 1 (3-weekly cycle)	39	45	9.9	Kim et al. 2008 [56]

ORR, overall response rate; MST, median overall survival time

reported analyses from a phase II study of a similar regimen for patients with advanced gastric cancer [51].

Capecitabine plus weekly docetaxel (docetaxel 36 mg/m² on days 1 and 8 and capecitabine 1000 mg/m² twice a day on days 1–14 every 3 weeks) achieved a 40.4% response rate and a median TTP of 4.5 months in a phase II study in patients with metastatic gastric cancer

[17]. The median OS time of 12 months was prolonged compared with the survival times reported for DF [15] and was similar to those reported for the other new-generation combinations [52].

Although the phase III First-Line Advanced Gastric Cancer (FLAGS) trial, designed to compare CF with S-1/CDDP, failed to show an advantage of S-1 in OS

compared with 5-FU in Western populations [53], the observed activity and tolerability of docetaxel with S-1 or capecitabine, together with the convenience of oral S-1 dosing, make these highly promising new regimens with the potential to improve survival in patients with advanced or recurrent gastric cancer. Several phase III studies to evaluate these regimens, such as the Japan-Korea Cooperative Study of Docetaxel/S-1 Versus S-1 in Advanced Gastric Cancer (START) are now ongoing; in 2010 the final results of the START study will be reported [54]. The future role of S-1 in gastric cancer could also be the inclusion of this oral drug in a three-drug regimen, making DCF or ECF better tolerated.

Combinations with oxaliplatin. A variety of clinical studies have suggested that both the activity and the toxicity of classical platinum-based chemotherapy in gastric cancer may be improved by the substitution of CDDP by oxaliplatin; thus, oxaliplatin would be another potent partner with docetaxel [2, 3, 6–8, 55].

Kim et al. [56] conducted a phase II study to evaluate the efficacy and safety of a combination regimen of docetaxel/oxaliplatin (docetaxel 65 mg/m² and oxaliplatin 120 mg/m² on day 1 every 3 weeks). The combination achieved promising results for ORR (45.2%; 95% CI, 32%–59%), median TTP (5.7 months; 95% CI, 4.3–7.2 months), and median OS (9.9 months; 95% CI, 7.8–12.0 months). Among 47 assessable cases, grade 3/4 neutropenia occurred in 11 patients (23.4%) and febrile neutropenia was observed in 7 patients (14.9%). Another docetaxel/oxaliplatin combination regimen (docetaxel 60 mg/m² followed by oxaliplatin 130 mg/m² on day 1 every 3 weeks) was also investigated as a second-line treatment after failure of fluoropyrimidine and platinum [57]. The docetaxel/oxaliplatin (DOCOX) regimen in 48 pretreated Chinese patients (46 assessable) demonstrated an ORR of 22.9% (95% CI, 0.9%–34.9%), median TTP of 4.4 months (95% CI, 3.4–5.4 months), and median OS of 7.2 months (95% CI, 6.6–12.1 months). Grade III/IV neutropenia was observed in 26% of the patients, and grade 3 thrombocytopenia and febrile neutropenia occurred in 4.3% and 6.5% of the patients. Docetaxel and oxaliplatin have modest activity with predictable hematologic toxicity when given as salvage therapy.

A triplet regimen, epirubicin/oxaliplatin/docetaxel, in metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma was also evaluated in a phase II study [58]. The regimen (epirubicin 50 mg/m², docetaxel 60 mg/m² followed by oxaliplatin 100 mg/m² on day 1 every 3 weeks) achieved an ORR of 47.5% (95% CI, 32%–63%), median TTP of 6.3 months (95% CI, 5.4–7.2 months), and median OS of 12.1 months (95% CI, 10.7–13.5 months). Grade 3/4 neutropenia occurred in 50% of the patients, with two episodes of febrile neutropenia

(5%). Nonhematologic grade 3 toxicities included sensory neuropathy (5%), vomiting and mucositis (5%), and diarrhea in one patient (2.5%). This combination is also active and well tolerated in patients with metastatic gastric or GEJ adenocarcinoma.

Al-Batran et al. [59] investigated the FLOT regimen, which incorporated docetaxel into a tolerable biweekly oxaliplatin-based chemotherapy regimen (oxaliplatin 85 mg/m², leucovorin 200 mg/m², and fluorouracil 2600 mg/m² as a 24-h infusion in combination with docetaxel 50 mg/m² on day 1 every 2 weeks). The phase II study demonstrated that the FLOT regimen had an acceptable toxicity profile, while response rates and median survivals of the patients were in the range of those reported with DCF. The study included 59 chemotherapy-naïve patients with metastatic gastric cancer, and provided an ORR of 50.9%, median PFS of 5.2 months, and an OS of 11.1 months. Frequent (>10%) grade 3 or 4 toxic effects in 54 assessable cases included neutropenia in 26 (48.1%), leukopenia in 15 (27.8%), diarrhea in 8 (14.8%), and fatigue in 6 (11.1%) patients, and complicated neutropenia was observed in 2 (3.8%) patients, only.

In addition to the above-mentioned regimens, a variety of possible oxaliplatin-containing regimens such as D-FOX (docetaxel/5-FU/oxaliplatin) are now being intensively investigated [12, 60].

Combinations with irinotecan (CPT-11). Irinotecan (CPT-11) is also active in gastric cancer, showing an ORR of 14%–25% as a single agent, which suggests the topoisomerase I inhibitor to be a possible partner of docetaxel [12, 60]. A doublet regimen, docetaxel/CPT-11, has been investigated by several study groups, but the observed clinical benefit is unlikely to be promising: the regimen had modest activity and was highly toxic. Park et al. [61] evaluated the efficacy and safety of a docetaxel/CPT-11 regimen (docetaxel 30 mg/m² and CPT-11 70 mg/m² on days 1 and 8 every 3 weeks) in chemo-naïve patients with metastatic gastric cancer (48 enrolled and 46 assessable). This study achieved an ORR of 45.7% (95% CI, 31.3%–60.1%), median TTP of 4.5 months (95% CI, 3.8–5.2 months), and median OS of 8.2 months (95% CI, 5.8–10.6 months). Grade 3/4 neutropenia developed in 57.4% of the patients, and febrile neutropenia/neutropenic infection in 19.1%. Nonhematologic toxicities were moderate; grade 3/4 diarrhea occurred in 19.1% of the patients; however, the toxicity was manageable with dose reduction. Sym et al. [62] studied a doublet regimen in a salvage treatment setting with different doses and schedules (CPT-11 160 mg/m² followed by docetaxel 65 mg/m² every 3 weeks). The doses of both CPT-11 and docetaxel were reduced to 120 mg/m² and 50 mg/m² due to unacceptable toxicity in the first ten patients. ORR, median TTP,

and median OS were 20.4% (95% CI, 9.1%–31.7%), 2.7 months (range, 2.1–69.1 months), and 8.9 months (95% CI, 6.6–11.3 months), respectively. Grade 3/4 toxicities included neutropenia (90%), febrile neutropenia (50%), asthenia (40%), and diarrhea (10%) with the higher dose and neutropenia (71%), febrile neutropenia (11%), diarrhea (24%), and asthenia (24%) with the lower dose. There were two possible treatment-related deaths.

Recently, weekly docetaxel, CDDP, and CPT-11 (TPC) was studied in patients with metastatic esophagogastric cancer by Enzinger et al. [63]. Based on the results in the phase I study, docetaxel 30 mg/m², CDDP 25 mg/m², and CPT-11 65 mg/m² were selected for the phase II trial, but the dose of CPT-11 was reduced to 50 mg/m² due to severe diarrhea. The phase II trial enrolled 56 patients with previously untreated, metastatic esophagogastric cancer, and demonstrated an ORR of 54%, median PFS of 7.1 months, and median survival of 11.9 months. At the final CPT-11 dose of 50 mg/m², grade 3 or higher toxicity included diarrhea (26%), neutropenia (21%), nausea (18%), fatigue (16%), anorexia (13%), and thrombosis/embolism (13%).

Combinations with biological agents. The incorporation of biological agents, such as cetuximab, bevacizumab, everolimus, and sunitinib, into combination regimens is another innovative approach [2–8, 64]. The optimum combination of these agents is now being intensively investigated, and high response and/or disease control rates have been reported, especially for combinations with epidermal growth factor receptor (EGFR)-targeted cetuximab, such as FOLCETUX (cetuximab alone following CPT-11/5-FU/leucovorin (FOLFIRI) regimen for a maximum of 24 weeks) [65, 66] and combinations with VEGF-targeted bevacizumab [67]. Various randomized phase III studies incorporating targeted agents, such as ToGA (Trastuzumab with Chemotherapy in HER2-Positive Advanced Gastric Cancer) and AVAGAST (Avastin in Gastric Cancer) in first-line regimens have recently been initiated [6, 64]. Combinations of biological agents with docetaxel or docetaxel-containing combinations have also been intensively studied. Among the biological agents, the monoclonal antibodies cetuximab and bevacizumab are the most investigated agents, despite there being sparse published data at present.

Although a study to evaluate a combination of docetaxel with cetuximab (400 mg/m² initial dose followed by 250 mg/m² weekly for maintenance) with docetaxel (30 mg/m² on days 1 and 8 every 3 weeks) in a salvage treatment setting suggested it had limited clinical benefit in terms of ORR, PFS, and OS [68], the incorporation of cetuximab (400 mg/m² initial dose fol-

lowed by 250 mg/m² weekly for maintenance) into a doublet docetaxel regimen (DOCETUX; docetaxel 75 mg/m² and CDDP 75 mg/m² every 3 weeks) showed hopeful results, with an ORR of 40.5% (one complete response) in the front-line setting [69]. The most common grade III/IV toxicities were neutropenia (45.8%), febrile neutropenia (22.9%), and anemia (6.25%); toxicities included fatigue (22.9%), hyponatremia (20%), hypokalemia (16%), skin reaction (31.3%), vomiting (8.3%), and stomatitis (6.3%). Based on these encouraging results, further phase II trials of first-line therapy with cetuximab in combination with capecitabine and CDDP or docetaxel and oxaliplatin are ongoing [12, 64].

For bevacizumab, Enzinger et al. [70] evaluated a combination regimen with docetaxel (bevacizumab 5 mg/kg days 1 and 15, docetaxel 35 mg/m² days 1, 8, and 15), and, further, a more aggressive combination (docetaxel 30 mg/m², CDDP 25 mg/m², CPT-11 50 mg/m² on days 1 and 8, bevacizumab 10 mg/kg on day 1, every 3 weeks) in advanced gastroesophageal cancer [12, 64, 70]. Despite a low ORR of 27% in the former regimen, the latter demonstrated a high ORR of 63% in the chemotherapy-naïve patient population, with well-tolerated toxicity.

A modified DCF regimen with bevacizumab (docetaxel 40 mg/m², 5-FU bolus 400 mg/m², leucovorin 400 mg/m², and infusional 5-FU 1000 mg/m² ×2 days, and bevacizumab 10 mg/kg day 1, CDDP 40 mg/m² on day 3) was also evaluated [12, 64]. The study achieved a significantly higher ORR of 71%, compared with that for DCF, with markedly less toxicity than DCF. However, with the bevacizumab combination, patients should be carefully monitored for gastrointestinal perforation. El-Rayes et al. [71] investigated a combination of docetaxel/oxaliplatin with bevacizumab (docetaxel 70 mg/m², oxaliplatin 75 mg/m², and bevacizumab 7.5 mg/kg every 3 weeks), and reported that this docetaxel/oxaliplatin/bevacizumab combination resulted in gastrointestinal perforation in two patients after cycle 2.

Future perspectives

As well as the other new-generation (third-generation) agents, docetaxel is now of key importance in the development of new-era systemic chemotherapy. Actually, the incorporation of docetaxel into gastric cancer chemotherapy has yielded a pivotal regimen, DCF, and a variety of regimens that could potentially become standard treatments in gastric cancer. Even so, the DCF regimen has substantial toxicity; optimization studies and the development of alternative docetaxel-containing regimens are now intensively ongoing. The

best partner for docetaxel in the treatment of gastric cancer remains unknown.

In Japan, S-1 is the most widely used drug for the treatment of gastric cancer, based on the results of the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study and a SPIRITS trial [11, 78]. Although differences between Asian and Western patients, such as the relatively low involvement of GE junction tumors in Asian populations and differences in S1 pharmacokinetics caused by CYP2C6 polymorphic differences are suggested, new-generation chemotherapy including S-1 is undoubtedly one of the most promising candidates as a standard treatment for advanced gastric cancer. As a partner of docetaxel, S-1 appears to be more suitable than other third-generation and biological agents. In fact, the reported activity and tolerability of several docetaxel/S-1 regimens make these combinations highly promising ones, with the potential to improve survival in patients with advanced or recurrent gastric cancer. The evaluation of docetaxel/S-1 regimens in large-scale and well-designed randomized phase III clinical trials in various settings, including the perioperative adjuvant setting, is eagerly awaited.

Along with extensive efforts directed toward developing more active docetaxel combination regimens, much attention has been focused on predictive biomarkers of the regimens [72, 73]. Pharmacogenomics is increasingly being recognized as an effective way to optimize therapy and the treatment dose for individuals, and the FDA has validated possible biomarkers and is using corresponding FDA-approved drug labels with three recommendation levels of testing: "required", "recommended", and "information only" (http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm) [4]. At present, however, there is no FDA-approved biomarker for the agents commonly used in gastric cancer chemotherapy, with the exception of C-KIT expression for imatinib mesylate in gastrointestinal stromal tumors. Even so, advances in pharmacogenomics in gastric cancer have provided a number of putative candidate markers for the prediction of tumor response to chemotherapies, including docetaxel and docetaxel-containing combination regimens [4, 72–77]. We look forward to obtaining more data from ongoing trials, and we believe that future large trials will provide the best chemotherapy and predictive biomarkers for indicating individual toxicity risks and therapeutic benefits in gastric cancer patients.

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