Review article

Combination chemotherapy of S-1 and taxanes in Korea

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Abstract

Various combination treatments incorporating S-1 are undergoing clinical trials in Korea, especially combinations with taxane, oxaliplatin, or irinotecan. In a phase I study to estimate the maximum tolerated dose of docetaxel in combination with S-1 administered at a fixed dose of 40 mg/m² twice daily on days 1–14 of each 3-week cycle in patients with advanced gastric cancer, 60 mg/m² docetaxel was declared to be the maximum tolerated dose. A phase I/II study of the same schedule of combination chemotherapy with S-1 plus docetaxel reported doses of S-1/docetaxel of 40/75 mg/m² as the maximum tolerated dose. In a phase I study of S-1 plus weekly docetaxel, the patients received variable doses of docetaxel administered intravenously over 1 h on days 1 and 8 and S-1 administered on days 1–14 of each 3-week cycle. The maximum-tolerated doses of S-1 and docetaxel were determined to be 45 mg/m² and 35 mg/m² in this study. A phase I/II study of docetaxel plus S-1 combination chemotherapy from Korea reported a response rate of 43.3%. Also, a phase II study of paclitaxel plus S-1 as first-line therapy in patients with advanced or relapsed gastric cancer showed an overall response rate of 49%. The most frequent significant toxicities in combination chemotherapies with taxane plus S-1 were neutropenia and febrile neutropenia. However, nonhematological toxicities were mild to moderate. A taxane plus S-1 combination regimen could be a new standard regimen for advanced gastric cancer, given its significant activity and favorable toxicity pattern.

Key words Gastric neoplasm · Docetaxel · Paclitaxel · S-1 · Combination chemotherapy

Introduction

Although the incidence and mortality rates of gastric cancer are decreasing on a worldwide basis, Korea

continues to have one of the highest incidence rates of gastric cancer [1]. According to the Korea Central Cancer Registry and Local Cancer Registries data, gastric cancer remains the leading malignancy in both sexes, although its incidence has decreased slightly [2]; the age-standardized incidence rate for gastric cancer was 58.6 per 100 000 for males and 30.8 per 100 000 for females from 1999 to 2001 [2]. Surgical resection is the only therapeutic modality capable of cure, and improvements in early diagnosis, preoperative assessment, and surgical techniques have increased the number of potentially curative resections over the past 20 years. However, despite these improvements, prognosis remains poor, with overall 5-year relative survival rates of approximately 20% in most areas of the world, except for Japan [3].

The reasons for this grim outlook are that both local and distant relapse, even after apparently complete resection, are common, and that many patients present with inoperable disease at the time of diagnosis. In such patients, chemotherapy is one of the main treatment strategies that are employed. Although previously it was not clear whether chemotherapy contributed to the survival of patients with unresectable advanced gastric cancer, recent studies that have compared patients who received chemotherapy with non-chemotherapy-treated patients (best supportive care; BSC) have demonstrated that chemotherapy improves survival in advanced gastric cancer [4–6].

The treatment of advanced gastric cancer in Korea has followed the leads given in the reports published in and the experiences of practitioners in other countries. In the 1980s, the 5-fluorouracil (5-FU), adriamycin, and mitomycin (FAM) regimen was adopted as a standard chemotherapy, and until the mid 1990s, clinical trials conducted in gastric cancer patients in Korea mainly replicated well-known therapeutic regimens or modified original protocols to improve toxicity profiles.

Clinical results of taxane use in Korea

Taxanes have been actively investigated in the context of gastric cancer chemotherapy in Korea, and the combination of paclitaxel, cisplatin, and 5-FU appears to be highly active, with acceptable toxicity [7], with an overall response rate of 51% and a complete response rate of 10% being achieved in 41 patients with advanced gastric carcinoma. Moreover, the combination of paclitaxel, infusional 5-FU, and leucovorin showed a response rate of 31.7% and a median survival of 60 weeks in 60 patients with advanced gastric cancer [8]. Promising results were also reported for various doses and schedules of paclitaxel and cisplatin, with overall response rates of 36.5% to 44% and median times to progression and overall survivals of 4.7 to 6.0 months and 10.8 to 12.1 months, respectively [9, 10]. In addition, paclitaxel plus carboplatin had a response rate of 22% in patients with advanced gastric cancer previously treated with 5-FU and platinum [11]. One study compared paclitaxel plus 5-FU with docetaxel plus 5-FU as first-line chemotherapies in patients with metastatic gastric cancer [12]. Although no significant difference was found in terms of their therapeutic efficacies, paclitaxel plus 5-FU was found to be associated with fewer grade 3 or 4 toxicities and a better quality of life [12].

Docetaxel (Taxotere; Sanofi-Aventis, Paris, France) is a semisynthetic taxoid derived from the European yew tree, *Taxus baccata* [13]. Docetaxel has more potent activity than the natural taxane paclitaxel in terms of the stabilization/hyperplasia of microtubules by facilitating microtubule protein polymerization, thereby inhibiting mitosis to display antitumor effects [14]. Docetaxel has shown encouraging activity in gastric cancer; the single-agent response rate ranged from 17% to 24%, with a mean of 19.1% (95% confidence interval [CI]; 14.3%–23.8%) [15]. Docetaxel at 75 mg/m² produced a response rate of 15.9% in Korean gastric cancer patients [16]. Interestingly, the response rate of docetaxel monotherapy was similar in chemotherapy-naïve and previously treated patients [17]. Several investigators have tried docetaxel plus cisplatin in patients with advanced gastric cancer, and achieved overall response rates of 17.1% to 43.5% and median survivals of 5.8 to 11.5 months [18–20]. Based on a synergism between docetaxel and 5-FU found in a preclinical study, docetaxel was administered with infusional 5-FU and low-dose leucovorin to 66 patients with advanced gastric cancer. A response rate of 34.2% was achieved in chemo-naïve patients and the rate was 14.2% in previously treated patients [21]. Various doses and combination schedules of docetaxel and capecitabine have also been examined in advanced gastric cancer. In a weekly docetaxel plus capecitabine trial, 55 patients received docetaxel (36 mg/m² intravenously), on days 1 and 8, and capecitabine (1000 mg/m²

orally twice per day), on days 1–14, in a 3-week schedule until progression occurred. The overall response rate and median survival were 40.4% and 12.0 months, respectively [22]. On the other hand, when docetaxel was administered every 3 weeks at 75 mg/m² with capecitabine at 1250 mg/m² twice daily on days 1–14, the response rate was much higher (60%), with a median survival of 10.5 months [23]. However, this combination treatment showed high incidences of stomatitis and hand-foot syndrome as dose-limiting toxicities, which prevented continuous treatment. When the capecitabine dosage was reduced to 1000 mg/m² in this regimen, the response rate fell to 43.8%, while the reduced capecitabine dosage reduced the incidence of hand-foot syndrome [24]. The phase III TAX 325 study, which enabled the registration of docetaxel in combination with cisplatin and intravenous 5-FU in Europe and the United States, demonstrated a superior response rate, time to progression, overall survival, clinical benefit, and quality of life over cisplatin and intravenous 5-FU in patients with advanced gastric cancer, and thus clearly demonstrated both the activity of docetaxel in this disease, and also the proof of principle of the benefit of adding docetaxel to standard regimens [25].

Clinical results of S-1 use in Korea

S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an oral fluoropyrimidine derivative that combines tegafur with two modulators of 5-FU metabolism, 5-chloro-2, 4-dihydroxypyridine (gimeracil) and potassium oxonate (oteracil), in a molar ratio of 1:0.4:1. Tegafur, an oral prodrug of 5-FU, is gradually converted to 5-FU and rapidly catabolized by dihydropyrimidine dehydrogenase (DPD) in the liver. Gimeracil inhibits the degradation of 5-FU by the inhibition of DPD. Oteracil is an orotate phosphoribosyl transferase (OPRT) inhibitor, which preferentially localizes in the digestive tract. This component of S-1 decreases the phosphorylation of 5-FU in the gastrointestinal mucosa and reduces the incidence and severity of diarrhea [26]. Phase II studies of S-1 monotherapy in patients with advanced gastric cancer showed overall response rates of 26%–49%, with the most relevant adverse effects being diarrhea in a European study and neutropenia in two Japanese studies [27–29]. Although a phase II study of S-1 alone produced a response rate of only 19.3% in Korea [30], which was much lower than that reported in Japan (44%–49%), an S-1 plus cisplatin combination demonstrated a response rate of 48%, with a favorable toxicity profile [31]. Various combination treatments incorporating S-1 are undergoing clinical trials in Korea, especially combinations of S-1 with a taxane, oxaliplatin, or irinotecan.

Combination chemotherapy of S-1 and taxanes in Korea

Docetaxel and S-1 have different modes of action and are highly synergistic in gastric cancer xenografts [32]. Also, the synergistic effects of docetaxel and S-1 were evident both in vivo and in vitro and could be explained by docetaxel's biochemical modulation of the expression and activity of the thymidylate synthase (TS), DPD, and OPR1 enzymes, which play key roles in the functional activities of 5-FU or S-1 [33]. The docetaxel/S-1 combination was active and well tolerated in phase I studies, a phase I/II study, and a phase II study in advanced gastric cancer, although the treatment schedules were slightly different [34–38]. The result of a recent phase II study in [38] patients with advanced gastric cancer (docetaxel 40 mg/m² administered intravenously over 1 h on day 1 and oral S-1 administered at a fixed dose of 40 mg/m² twice daily on days 1–14 of each 3-week cycle) was highly promising (a response rate of 56.3% with a median survival time of 14.3 months), with tolerable toxicities; accordingly, a multinational randomized phase III study comparing S-1 alone versus docetaxel plus S-1 was planned at this dose and schedule. The relatively low dose of docetaxel recommended in that study, possibly as a result of the conservative definitions used for dose-limiting-toxicities (DLTs) in the previous phase I study [37], (i.e., the DLTs were mild compared with the definitions used in other phase I studies) [37] resulted in the need to conduct a further dose-finding phase I trial of the docetaxel and S-1 combination.

Investigators from St. Vincent's Hospital and Korea University Anam Hospital conducted a phase I study for the escalation of docetaxel with a fixed dose of S-1 in advanced gastric cancer [39]. The primary endpoint of this study was the determination of 3-weekly docetaxel dose feasibility in the combination of docetaxel and oral S-1 administered at a fixed dose of 40 mg/m² twice daily on days 1–14 of each 3-week cycle in patients with advanced gastric cancer. Between October 2004 and June 2005, 13 patients from the two institutes were enrolled in this study. Patients received variable doses of intravenous docetaxel administered intravenously over 1 h on day 1 and oral S-1 administered at a fixed dose of 40 mg/m² twice daily on days 1–14 of each 3-week cycle. Three doses of S-1 were established according to body surface area (BSA; BSA < 1.25 m², 80 mg/day; 1.25 m² ≤ BSA < 1.5 m², 100 mg/day; and 1.5 m² ≤ BSA, 120 mg/day). The initial starting dose of docetaxel was 40 mg/m² (dose level 1), and stepwise dose increases to 50, 60, and 70 mg/m² were planned for successive patient cohorts (dose levels 2, 3, and 4, respectively). DLTs were defined as follows: (1) grade 3 febrile neutropenia (absolute neutrophil count < 1000/μl with

fever ≥ 38.5 °C); (2) grade 4 neutropenia lasting for 7 days or longer; (3) grade 4 thrombocytopenia or thrombocytopenic bleeding; (4) grade 3/4 nonhematological toxicities other than nausea/vomiting and alopecia.

Initially, 4 patients were allocated at dose level 1 (docetaxel 40 mg/m²; first cohort of level 1). However, 1 patient dropped out after the first cycle of treatment due to violation of eligibility criteria. The 3 other patients at dose level 1 did not experience DLT. Therefore, the dose of docetaxel was increased, and the initial 3 patients at dose level 2 (docetaxel 50 mg/m²; first cohort of level 2) were enrolled. One patient in this cohort developed grade 3 elevation of alkaline phosphatase and another patient had prolonged grade 4 neutropenia. To evaluate toxicity in a larger group at dose level 2, 3 additional patients were enrolled (second cohort of level 2). No patient in this cohort developed DLT. Thus, 2 of 6 patients at dose level 2 developed DLT and the initial 3 patients at dose level 3 (docetaxel 60 mg/m²; first cohort of level 3) were enrolled. All 3 patients at this dose level developed DLT (1 with grade 4 metabolic acidosis; 1 with grade 3 gastrointestinal hemorrhage; and 1 with grade 3 febrile neutropenia, grade 3 mucositis, and grade 3 diarrhea), and this level was declared to be the maximum tolerated dose (MTD). Hence, level 2 (docetaxel 50 mg/m²) was declared to be the recommended dose (RD) for the next study. As 9 of the 13 enrolled patients responded to treatment, the overall objective response rate was 69.2% (95% CI, 44.1%–94.3%).

Grade 4 neutropenia occurred in two of four patients at docetaxel 40 mg/m², in four of six patients at docetaxel 50 mg/m², and in one of three patients at docetaxel 60 mg/m². Grade 3 and grade 4 thrombocytopenia developed in one patient at 40 mg/m² and in one patient at 60 mg/m² of docetaxel, respectively. Grade 3 or 4 anemia was also noted in two of four and two of three patients at 40 mg/m² and 60 mg/m² of docetaxel, respectively. The main nonhematological toxicities encountered were anorexia, abdominal pain, nausea/vomiting, abnormal hepatic function, and infection without neutropenia. Most nonhematological toxicities were of mild to moderate intensity. Grade 3 nonhematological toxicities were observed in five patients (diarrhea and infection without neutropenia in two patients each and one patient with nausea/vomiting).

Zang et al. [40] conducted a phase I/II study to define the maximum tolerated dose (MTD) and recommended dose (RD) of the same schedule of S-1 plus docetaxel combination chemotherapy as that used in the study above [39] in patients with advanced or recurrent gastric cancer. Patients received variable doses of intravenous docetaxel administered intravenously over 1 h on day 1 and oral S-1 administered at variable doses twice daily

on days 1–14 of each 3-week cycle. Each cohort of 3 patients was treated with escalating doses of S-1/docetaxel at 30/60 mg/m² (level 1), 40/60 mg/m² (level 2A), 30/75 mg/m² (level 2B), and 40/75 mg/m² (level 3). A total of 56 patients were enrolled in this study (15 patients for the phase I study, 6 for a phase I study of elderly patients, and 35 for the phase II study). At level 3, 2 of the 3 enrolled patients developed DLTs (grade 4 febrile neutropenia and grade 4 neutropenia with grade 3 stomatitis, respectively). Therefore, level 3 and level 2B were declared to be the MTD and RD, respectively. However, 2 patients (aged 66 and 64 years) developed fatal toxicities during the initial phase II study. Zang et al. conducted an additional phase I study for elderly patients (age, more than 60 years) with level 2A and no DLTs occurred at this level. Hence, level 2A was determined as the RD for elderly patients. The response rate of the phase II study was 43.3% (95% CI, 26%–61%). The most common grade 3/4 toxicities were neutropenia (41.1%), leucopenia (35.7%), and febrile neutropenia (26.8%).

Park et al. [41] conducted a phase I study to define the MTD and DLT of S-1 plus weekly docetaxel in patients with metastatic gastric cancer. Patients received variable doses of docetaxel administered intravenously over 1 h on days 1 and 8 and oral S-1 administered at variable doses twice daily on days 1–14 of each 3-week cycle. Each cohort of 3 patients was treated with escalating doses of S-1/docetaxel at 30/25 mg/m² (level 1), 35/25 mg/m² (level 2), 35/30 mg/m² (level 3), 40/30 mg/m² (level 4), 40/35 mg/m² (level 5), 45/35 mg/m² (level 6), and 45/40 mg/m² (level 7). A total of 222 cycles of treatment were administered to 30 patients. At dose level 1, one of the first 3 patients experienced a DLT (grade 3 aspartate aminotransferase [AST] elevation), but none of the 3 additional patients experienced a DLT. During dose escalation, DLT did not develop until dose level 7, at which 2 of 3 patients experienced DLTs (grade 3 febrile neutropenia and grade 3 infection with neutropenia with grade 3 stomatitis/anorexia). Therefore, the next 3 patients were entered at dose level 6, but 2 of these patients (2 of a total of 6) had DLTs (grade 3 diarrhea with grade 3 fatigue and febrile neutropenia with grade 3 anorexia/fatigue). An additional 3 patients were entered at dose level 5, but 1 (1 of a total of 6) experienced a DLT (gastric perforation at the tumor site on the first day of cycle 1). Hence, the MTD and RD of S-1 plus weekly docetaxel were determined to be 45/35 mg/m² (level 6) and 40/35 mg/m² (level 5), respectively, in this study.

The result of a phase II study of this regimen was reported in 2007 at the American Association for Cancer Research Annual Meeting [42]. Out of 51 evaluable patients, the overall response rate was 64.7% (95% CI, 51.6%–77.8%) including one complete response. With

a median follow-up period of 8.4 months, the median progression-free survival was 6.2 months and median overall survival was not reached. The relative dose intensities of docetaxel and S-1 were 91% and 85%, respectively. The most common grade 3/4 toxicities were neutropenia (27.5%) and febrile neutropenia (17.6%). Grade 3 nonhematological toxicities included infection without neutropenia (21.6%), fatigue (9.8%), liver enzyme elevation (7.8%), constipation (5.9%), and diarrhea (3.9%).

A phase II study of paclitaxel plus S-1 as first-line therapy in patients with advanced or relapsed gastric cancer was conducted as a multicenter study under the auspices of the Korean Cancer Study Group and the result was reported at the 2007 American Society of Clinical Oncology annual meeting [43]. Patients received 70 mg/m² of paclitaxel administered intravenously on days 1 and 8 and oral S-1 administered at 35 mg/m² twice daily on days 1–14 of each 3-week cycle. A total of 56 patients were enrolled. Out of 53 evaluable patients, 1 had a complete response (2%), and 25 had partial responses (47%), giving an overall response rate of 49% (26/56). With a median follow-up period of 9.6 months, the median progression-free survival was 7.7 months and median survival was 14.6 months. The relative dose intensities of paclitaxel and S-1 were 93% for each. The most common cause of a delayed cycle was neutropenia and the most common cause of dose reduction was diarrhea. The most common grade 3/4 toxicities were neutropenia (19%) and febrile neutropenia (5%). Most nonhematological toxicities were of mild to moderate intensity. Grade 3 nonhematological toxicities were observed in 10% of the patients (diarrhea in 4%, stomatitis in 4%, and anorexia in 2%). In this study, paclitaxel and S-1 combination chemotherapy showed significant activity with manageable and tolerable toxicities in patients with advanced gastric cancer.

Future prospects for combination chemotherapy with S-1 and taxanes

Several studies, from Europe, the United States, Japan, and Korea, have assessed docetaxel monotherapy in the treatment of advanced gastric cancer, with generally consistent results. While four studies from Europe and the United States administered docetaxel at a dosage of 100 mg/m² [44–47], the Japanese studies used docetaxel at 60 mg/m² [48, 49] and a Korean phase II study used a dose of 75 mg/m² [16]; in these seven studies, the response rate varied in a narrow range, from 17% to 24%, despite the varying dosages.

Two phase I studies of combination therapy with docetaxel and S-1 were conducted in Japan (Table 1).

One study (Yoshida et al. [37]) adopted an every-3-week schedule with S-1 administration for 2 weeks and the other study used an every-4-week schedule of S-1 with 2 weeks on and 2 weeks off [36]. In these two studies, the RD of docetaxel was 40 mg/m² every 3 or 4 weeks in combination with S-1 administered at a fixed dose of 40 mg/m² twice daily on days 1–14. Considering the definition of DLTs in the study by Yoshida et al. [37], there is a possibility that the reported RD may have been a suboptimal one, because most grade 4 neutropenia lasting for less than 7 days is usually considered to be manageable. Actually, Yoshida et al. [37] reported that the MTD was reached at level 2 (docetaxel 50 mg/m² plus oral S-1 administered at a fixed dose of 40 mg/m² twice daily on days 1–14 of each 3-week cycle) in three out of six patients, and grade 4 neutropenia was the DLT in two patients. In the other Japanese phase I study of docetaxel plus S-1 [36], the DLTs were defined as grade 4 neutropenia lasting for 5 days or longer; grade 4 neutropenia with fever; grade 4 thrombocytopenia; grade 3/4 nonhematological toxicities other than nausea/vomiting, anorexia, and general fatigue; and any grade 4 hematological toxicity during S-1 administration. The numbers of patients showing DLTs in this study were: one patient with grade 3 infection associated with grade 3 neutropenia and two patients with grade 4 neutropenia during S-1 administration at dose level 1 (docetaxel 50 mg/m² plus oral S-1 administered at a fixed dose of 40 mg/m² twice daily on days 1–14 of each 4-week cycle). The results from these two phase I studies suggested that the development of grade 4 neutropenia was frequent at the dose level of docetaxel 50 mg/m² plus oral S-1 administered at a fixed dose of 40 mg/m² twice daily on days 1–14 of a 3- or 4-week cycle, but the duration of severe neutropenia was not specified.

According to the study by Kim et al. [39], carried out in patients with advanced gastric cancer, only two out of five patients with DLT had DLT related to significant neutropenia (one patient with grade 4 neutropenia for more than 7 days and one patient with grade 3 febrile neutropenia). Also, six patients, who were enrolled at the dose level of docetaxel 50 mg/m² plus S-1 40 mg/m² twice daily on days 1–14 of each 3-week cycle, tolerated 39 cycles of treatment without dose modification. The mean dose intensity of docetaxel was 15.5 mg/m² per week, which supports the idea that docetaxel 50 mg/m² plus S-1 40 mg/m² twice daily on days 1–14 of each 3-week cycle would be a tolerable dosage in this patient group. A phase I/II study conducted in Korea reported that the optimal docetaxel dosage would be 60–75 mg/m² plus S-1 40 mg/m² twice daily on days 1–14 of each 3-week cycle [40]. In a phase I study, which adopted weekly docetaxel administration with S-1 daily on days 1–14 of each 3-week cycle, the

recommended dose intensity of docetaxel was 23.3 mg/m² per week. However, grade 4 neutropenia still developed in two of four patients at the dose level of docetaxel 40 mg/m² plus S-1 40 mg/m² twice daily on days 1–14 of each 3-week cycle; clinical efficacy was noted at this dose level. Hence, Korean investigators agreed to adopt docetaxel 40 mg/m² on day 1 plus S-1 40 mg/m² twice daily on days 1–14 of each 3-week cycle, as an experimental arm to be compared with S-1 40 mg/m² twice daily monotreatment on days 1–28, every 6 weeks, in a phase III study in patients with advanced gastric cancer. We are awaiting the final result of this phase III study comparing S-1 alone to docetaxel plus S-1 in patients with advanced gastric cancer in Japan and Korea (in which patient enrollment has just finished), to confirm the advantage of docetaxel in terms of response and survival.

The clinical efficacy of combination chemotherapy with S-1 and taxanes shows that this combination is highly active. Two phase I/II studies of docetaxel plus S-1 combination chemotherapy, from Japan and Korea, reported a response rate of 45.7% (21/46), with two complete responses [36] and a response rate of 43.3% [40], respectively (Table 1). Yoshida et al. [38] reported a response rate of 56.3% (27/48) with docetaxel 40 mg/m² on day 1 plus S-1 40 mg/m² twice daily on days 1–14 of each 3-week cycle, which was similar to our study findings [39]. Also, in a phase II study of paclitaxel plus S-1 as first-line therapy in patients with advanced or relapsed gastric cancer [43], the response rate was 46% (26/56), including one complete response. These response rates are the most favorable of those that have been reported in the treatment of advanced gastric cancer. Although the determination of efficacy was not the primary purpose of phase I studies, and the number of patients was small, it is highly notable that the response rate of the docetaxel plus S-1 combination chemotherapy was impressively high. The overall objective response rates in Korean phase I studies using an S-1 plus docetaxel combination were 69.2% (95% CI, 44.1%–94.3%) [39] and 65.5% (95% CI, 48.2%–82.8%) [41].

The most frequent significant toxicities in taxane plus S-1 combination chemotherapy were neutropenia and febrile neutropenia. However, the nonhematological toxicities were of mild to moderate intensity. In clinical practice, nonhematological toxicities are more difficult to manage than uncomplicated neutropenia, but if the nonhematological toxicities are mild to moderate, patients can tolerate chemotherapy of long duration without delay or interruption of treatment.

We conclude that a taxane plus S-1 combination regimen could be a new standard regimen for advanced gastric cancer, given its significant activity and favorable toxicity pattern.

Table 1. Results of phase I/II studies using docetaxel plus S-1 combination chemotherapy in advanced gastric cancer

	Yoshida et al. [37]	Yamaguchi et al. [36]	Kim et al. [39]	Zang et al. [40]	Park et al. [41]
No. of patients	9 (phase I)	9 (phase I)/ 46 (phase II)	13 (phase I)	21 (phase I)/ 35 (phase II)	30 (phase I)
MTD					
Docetaxel	50 mg/m ² q 3 weeks	50 mg/m ² q 4 weeks	60 mg/m ² q 3 weeks	75 mg/m ² q 3 weeks	35 mg/m ² , Days 1 & 8 q 3 weeks
S-1	40 mg/m ² bid for 2 weeks q 3 weeks	40 mg/m ² bid for 2 weeks q 4 weeks	40 mg/m ² bid for 2 weeks q 3 weeks	40 mg/m ² bid for 2 weeks q 3 weeks	45 mg/m ² bid for 2 weeks q 3 weeks
DLT	Neutropenia, allergic reaction	G4 neutropenia, G3 infection with neutropenia	G3 GI bleeding, G4 metabolic acidosis, G3 febrile neutropenia	G4 febrile neutropenia, G4 neutropenia with G3 stomatitis	G4 febrile neutropenia, G3 diarrhea, G3 febrile neutropenia with G3 fatigue
Response rate	NS	45.7% (2 CR, 19 PR)	69.2% (9 PR)	43.3% (15 PR)	65.5% (2 CR, 17 PR)

MTD, maximum tolerated dose; DLT, dose-limiting-toxicity; G, grade; NS, not stated; CR, complete response; PR, partial response

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