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**Non-platinum-based chemotherapy for treatment of advanced gastric cancer: 5-fluorouracil, taxanes, and irinotecan**

Kang BW *et al*. Non-platinum-chemotherapy for AGC

Byung Woog Kang, Jong Gwang Kim, Oh-kyoung Kwon, Ho Young Chung, Wansik Yu

**Byung Woog Kang, Jong Gwang Kim,** Department of Hematology/Oncology, Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu 702-210, South Korea

**Oh-kyoung Kwon, Ho Young Chung, Wansik Yu,** Department of Surgery, Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu 702-210, South Korea

**Author contributions:** Kang BW and Kim JG performed the majority of the study and wrote the manuscript; Kwon OK, Chung HY, and Yu W conceived the study and finalized the revision; all authors read and approved the final manuscript.

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**Correspondence to: Jong Gwang Kim, MD, PhD,** Department of Hematology/Oncology, Kyungpook National University Hospital, Kyungpook National University School of Medicine, 807 Hogukno, Buk-gu, Daegu 700-712, South Korea. jkk21c@knu.ac.kr

**Telephone:** +82-53-2003521 **Fax:** +82-53-2002029

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**Abstract**

Despite numerous advances in treatment options, advanced gastric cancer (AGC) is a major public health issue and the leading cause of cancer-related deaths. Cisplatin is one of the most effective broad-spectrum anticancer drugs for AGC and a doublet combination regimen of either cisplatin-based or 5-fluorouracil (5FU)-based chemotherapy is generally used for treatment of patients with AGC. However, there is still no consensus on the best regimen for treating AGC. Recently, various new chemotherapeutic agents, including oral 5FU, taxanes, and irinotecan, have been identified as improving the outcomes for AGC when used in single agent or combination with non-platinum doublet chemotherapy. Nonetheless, it is still unclear whether non-platinum-based chemotherapy is a viable treatment option for patients with AGC. Accordingly, this review focuses on the efficacy and tolerability of non-platinum-based chemotherapy for patients with AGC.

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**Key words**: Gastric cancer; Cisplatin; 5-fluorouracil; Taxane; Irinotecan

**Core tip**: Although the platinum-based chemotherapy is adopted widely nowadays in spite of numerous side effects, there is still no standard treatment for palliative chemotherapy of advanced gastric cancer. The current review assessed the efficacy and tolerability of non-platinum-based chemotherapy as first-line palliative treatment in patients with inoperable advanced gastric cancer. The results showed that non-platinum-based chemotherapy including 5-fluorouracil, taxanes, and irinotecan, would seem to be as effective and tolerable as traditional platinum-based chemotherapy.

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**INTRODUCTION**

Advanced gastric cancer (AGC) is a major public health issue and the leading cause of cancer-related deaths, with a 5-year survival of only 20%[[1-3](#_ENREF_1)]. Despite numerous advances in treatment options, the prognosis for AGC remains dismal as most patients are in an advanced or inoperable stage at the time of diagnosis. One of the most important treatment modalities is systemic chemotherapy. A recent phase III trial showed that the addition of trastuzumab to a cisplatin–based chemotherapy significantly improved the survival of patients with human epidermal receptor 2 (HER2)-positive AGC[[4](#_ENREF_4)]. However, the frequency of HER2 overexpression is low (10%-20%), and there is no widely accepted first-line treatment for HER2-negative AGC.

Cisplatin is a small-molecule platinum compound forming intrastrand cross-links that activate the apoptotic pathway, resulting in cell death[[5](#_ENREF_5)]. Cisplatin is also one of the most effective broad-spectrum anticancer drugs for AGC. Generally, a doublet combination regimen of either cisplatin-based or 5-fluorouracil (5FU)-based chemotherapy is used for treating AGC[[6](#_ENREF_6)]. While a cisplatin-based combination has been found to be marginally superior to other combinations, the benefit is still disappointing with a response rate below 50% and high rate of toxicity[[7](#_ENREF_7)].

The significant toxicity of cisplatin, which often results nausea, vomiting, nephrotoxicity, and neurotoxicity, can also affect the final treatment outcomes and quality of life as the majority of patients present in an advanced stage. Plus, the effect of cisplatin-based chemotherapy has been found to vary depending on the tumor biology, where resistance markedly reduces its clinical effectiveness[[8](#_ENREF_8)]. Interestingly, the introduction of new agents, such as oral 5FU, taxanes, and irinotecan, has provided improved treatment outcomes for patients with AGC. In a recent meta-analysis by Chen *et al*[[9](#_ENREF_9)], combination regimens with such agents achieved a similar response rate and overall survival to platinum-based regimens. The toxicity of non-platinum-based regimens is also significantly lower in terms of hematologic toxicity, vomiting, and neurotoxicity. Nonetheless, it is still unclear whether non-platinum-based chemotherapy is a viable treatment option for patients with AGC. Accordingly, this review focuses on the efficacy and tolerability of non-platinum-based chemotherapy for patients with AGC.

**ROLE OF PLATIMUN-BASED CHEMOTHERAPY IN AGC**

Platinum-based doublet chemotherapy, typically cisplatin in combination with either infusional 5FU or an oral 5FU, such as S-1 or capecitabine, is current standard practice in many countries[[1](#_ENREF_1)]. In a randomized phase III trial (SPIRITS trial)[[10](#_ENREF_10)], 298 patients with AGC were randomized to S-1 plus cisplatin and S-1 alone. Median progression-free survival (PFS) (6.0 mo *vs* 4.0 mo) and overall survival (OS) (13.0 mo *vs* 11.0 mo) were significantly longer in the combination group. Response was also higher with S-1 (54% *vs* 31%). Based on this trial, S-1 plus cisplatin combination regimen has been established as a standard treatment for AGC in Japan. Two phase III trials have compared the efficacy and safety of cpaecitabine-based and 5FU-based combinations. In Western countries, the REAL-2 trial was a randomized multicenter phase III study comparing capecitabine with 5FU and oxaliplatin with cisplatin in 1003 patients with AGC[[11](#_ENREF_11)]. Although 30% of patients had an esophageal cancer, results from this study suggest that capecitabine and oxaliplatin are as effective as 5FU and cisplatin, respectively. Another phase III randomized trial (ML17032 trial) evaluated the combination of capecitabine and cisplatin *vs* the combination of 5FU and cisplatin in patients with AGC[[12](#_ENREF_12)]. Capecitabine and cisplatin combination was met the primary endpoint of non-inferiority of PFS (5.6 mo *vs* 5.0 mo). Median OS (10.5 mo *vs* 9.3 mo) and severity of adverse events were comparable in both groups. Consequently, oral 5FU (capeciatbine or S-1) and platinum-based combination has been widely accepted as one of the first choices for treatment in patients with AGC over the world.

**SINGLE-AGENT CHEMOTHERAPY**

A previous meta-analysis demonstrated a significant survival benefit related to the combination-arm when compared with the single-arm[[3](#_ENREF_3)]. However, in most previous studies, 5FU has only been evaluated as a single-agent chemotherapy. Plus, several new drugs, such as oral 5FU, taxanes, and irinotecan, have also only been evaluated as single agents in terms of their efficacy and tolerability when treating AGC.

***5FU (intravenous)***

In the early 1980s, 5FU alone was evaluated an active single agent for patients with AGC[[13](#_ENREF_13)]. Subsequently, 5FU incorporated with leucovorin was also investigated[[14](#_ENREF_14),[15](#_ENREF_15)]. However, while these studies reported a 19%-48% objective response rate and tolerable toxicity profiles, more than half the patients had other types of gastrointestinal malignancies. A randonmized phase II trial by Barone *et al*[[16](#_ENREF_16)] compared a combination of 5FU and leucovorin with a cisplatin-containing regimen (cisplatin, etoposide, and epirubicin), where the median response duration was 8.8 and 8.3 mo, respectively. Thereafter, 5FU alone has been used as the reference arm in randomized phase III trials. The North Central Cancer Treatment Group compared 3 arms (5FU alone *vs* 5FU plus adriamycin *vs* 5FU, adriamycin, and methotrexate), however, there was no significant difference in the treatment outcomes[[17](#_ENREF_17)]. Similarly, in Japan, two randomized trials found no survival advantage between a cisplatin-based chemotherapy (5FU plus cisplatin or irinotecan plus cisplatin) and FU alone (7.1 mo *vs* 7.3 mo; 10.8 mo *vs* 12.3 mo)[[18](#_ENREF_18),[19](#_ENREF_19)]. Although the cisplatin-based chemotherapy produced a higher response rate and PFS, 5FU alone was associated with less toxicity.

***5FU (oral)***

Oral 5FU agents, such as capecitabine and S-1, are commonly used for AGC and have several advantages, including the possibility of continuous exposure to 5FU at the tumor site and minimized systemic exposure to 5FU, thereby reducing the toxicity and improving the convenience and quality of life[[20](#_ENREF_20),[21](#_ENREF_21)]. The activity of capecitabine has already been tested in phase II studies, which resulted in a response rate of 6% to 32%[[22](#_ENREF_22)]. In two early phase II studies conducted in Korea and Japan, capecitabine showed a median survival of 8-10 mo and response rate of approximately 20%-30%[[23](#_ENREF_23),[24](#_ENREF_24)]. Meanwhile, in another study with 704 patients, Boku *et al*[[18](#_ENREF_18)] demonstrated the non-inferiority of S-1 alone and superiority of irinotecan plus cisplatin over 5FU alone. For the primary endpoint, the PFS for S-1 was not inferior to that for 5FU (4.2 mo *vs* 2.9 mo, *P* < 0.001), and there was even a trend suggesting the superiority of S-1 over 5FU alone. The two arms were also comparable as regards adverse events, meaning that S-1 is an acceptable alternative to 5FU alone. Another important factor is that these two agents can be considered as an option for elderly patients or patietns with a poor performance status. In a phase II trial using S-1 for patients with a poor performance status and intolerance of combination chemotherapy, the results showed that S-1 is an active and safe drug with a response rate of 12%[[25](#_ENREF_25)]. Meanwhile, capecitabine was directly compared to S-1 in a randomized phase II trial with 91 elderly patients[[26](#_ENREF_26)]. In this case, the two agents (capecitabine *vs* S-1) were found to be comparable in terms of the response rate (27.2% *vs* 28.9%), median time to progression (4.7 mo *vs* 4.2 mo), OS (9.5 mo *vs* 8.2 mo), and treatment-related toxicity. Therefore, the above findings suggest that oral 5FU agents can be used for patients where platinum agents are contraindicated.

***Taxanes***

Taxanes (paclitaxel or docetaxel) disrupt the microtubule function and inhibit the process of cell division, and have shown encouraging activity in the treatment of AGC[[27](#_ENREF_27),[28](#_ENREF_28)]. Several studies have already investigated the sue of paclitaxel monotherapy for AGC and found response rates ranging from 17% to 28%[[28](#_ENREF_28)]. When investigating the efficacy of paclitaxel every 3 wk as a first-line treatment for AGC patients, Ajani *et al*[[29](#_ENREF_29)] found that a dose of 200 mg/m2 was generally well tolerated, produced a response rate of 17%, and the median survival was 8 mo. Meanwhile, when using a weekly dose of paclitaxel at 80 mg/m2, the response rate was 17.6% and the median survival was 7.3 mo[[30](#_ENREF_30)]. Docetaxel monotherapy has also been assessed for AGC patients in several phase II studies [[31](#_ENREF_31)]. When using a dose of 60-100 mg/m2 every 3 wk[[31-33](#_ENREF_31)], the response rate was 15% to 25% and the median survival ranged from 7.5 to 11.0 mo. While the most common adverse event was neutropenia, the incidence of neturopenic fever was very low. Therefore, despite the varying response rates, the overall outcome for taxanes were similar to the single-agent activity observed with most conventional drugs, making, taxanes an appropriate option for AGC.

***Irinotecan***

Irinotecan prevent DNA from unwinding by inhibiting topoisomerase I[[34](#_ENREF_34)]. Multiple trials have already shown good tolerance and promising results when using irinotecan as a single therapy for AGC, including response rates from 14% to 20% and a median survival of approximately 7 mo[[35](#_ENREF_35),[36](#_ENREF_36)]. As regards toxicity, the most common grade 3-4 toxicities were diarrhea (20%-30%) and neutropenia (23%-38.5%). Thus, despite a slightly higher response rate than with conventional agents, the toxicity of irinotecan remains a concern. Nonetheless, irinotecan can still be considered as an alternative single agent when a platinum-based therapy cannot be delivered.

**COMBINATION CHEMOTHERAPY**

In clinical trials, various new chemotherapeutic agents, including oral 5FU, taxanes, and irinotecan, have been identified as improving the outcomes for AGC when used in combination with non-platinum doublet chemotherapy.

For example, when studying the combination of 5FU plus anthracycline in conjunction with mitomycin or methotrexate, the initial reports showed high response rates of 30% to 60% and significantly improved survival with the addition of anthracycleins when compared to cisplatin and 5FU alone. However, the survival benefits were not consistent in a meta-analysis[[2](#_ENREF_2),[6](#_ENREF_6),[17](#_ENREF_17),[37-39](#_ENREF_37)]. Meanwhile, oral 5FU plus cisplatin or oxaliplatin combinations have been found to be more effective than the conventional regimen of cisplatin with 5FU alone[[12](#_ENREF_12),[13](#_ENREF_13)]. Thus, the questionable efficacy of adding anthracyclines has resulted in a worldwide decrease in their use.

Various combinations of oral 5FU agents (capecitabine or S-1) and taxanes or iriontecan have already been used in experimental models and, despite the absence of platinum agents, such combinations have been found to enhance the anticancer activity and overcome the resistance to each agent[[40-42](#_ENREF_40)]. Thus, several phase II studies have since investigated these combinations (Table 1), including capecitabine plus taxanes, capecitabine plus irinotecan, S-1 plus taxanes, and S-1 plus irinotecan, as the backbone of combination chemotherapy without a platinum agent. And the results were promising, with an overall response rate of 37%-52%, and median overall survival of 8-16 mo[[43-55](#_ENREF_43)]. Although a direct comparison is difficult due to the limitation of randomized phase II studies, three studies demonstrated comparable outcomes to cisplatin-containing chemotherapy in terms of the response rate, survival, and toxicity[[44](#_ENREF_44),[46](#_ENREF_46),[54](#_ENREF_54)]. The combination of docetaxel and irinotecan without cisplatin was also tested in a phase II trial, where doses of docetaxel 40 mg/m2/d and irinotecan 100 mg/m2/d on a 3-wk cycle provided an acceptable safety profile and modest activity with a response rate of 26% [[56](#_ENREF_56)]. In addition, the combination of irinotecan, 5FU, and leucovorin (FOLFIRI) has been shown to be active and well tolerated in patients with AGC[[57](#_ENREF_57),[58](#_ENREF_58)]. Therefore, based on the results of these trials, an irinotecan-containing regimen can be considered as a suitable alternative to a platinum combination.

A recent meta-analysis by Chen *et al*[[9](#_ENREF_9)] evaluated the efficacy and tolerability of platinum *vs* non-platinum chemotherapy as a first-line palliative treatment for patients with inoperable AGC. Based on 3680 patients in 27 trials, where 8 trials used pooled estimates for OS, the final hazard ratio for OS of 1.07 (95%CI: 0.88-1.30) showed no significant difference between the platinum-based and the non-platinum-based therapies containing new-generation agents. However, the occurrence of most adverse events was higher in the platinum-arm, except for diarrhea, and most importantly, toxic death rate and nephrotoxicity were much higher in the platinum-arm. Therefore, the combination regimens including new-generation agent showed a similar impact on survival and better tolerability.

**CONCLUSION**

Cisplatin-based and 5FU-based combinations are both widely used for AGC, yet there is no consensus on the best regimen. Predicting the response to each chemotherapeutic agent is difficult and the treatment outcomes vary in previous clinical studies. Plus, when determining the appropriate chemotherapy, assessing the severity of the disease and the toxicity related to a particular chemotherapy are both essential to improve outcome and relieve substantial toxicity. In the current review, newer agents, such as oral 5FU, taxanes, or irinotecan-based chemotherapy, would seem to be as effective and tolerable as traditional platinum-based chemotherapy. Accordingly, these newer agents should be considered as a preferred option for first-line chemotherapy in the case of AGC, especially for patients where platinum-based chemotherapy in contraindicated. Furthermore, additional trials are needed to define the benefits of these agents in patients with AGC.

**REFERENCES**

1 **Price TJ**, Shapiro JD, Segelov E, Karapetis CS, Pavlakis N, Van Cutsem E, Shah MA, Kang YK, Tebbutt NC. Management of advanced gastric cancer. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 199-208; quiz 209 [PMID: 22375525 DOI: 10.1586/egh.11.103]

2 **Wagner AD**, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; **24**: 2903-2909 [PMID: 16782930]

3 **Wagner AD**, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, Fleig WE. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010; : CD004064 [PMID: 20238327 DOI: 10.1002/14651858.CD004064.pub3]

4 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210]

5 **Siddik ZH**. Cisplatin: mode of cytotoxic action and molecular basis of resistance. *Oncogene* 2003; **22**: 7265-7279 [PMID: 14576837]

6 **Pasini F**, Fraccon AP, DE Manzoni G. The role of chemotherapy in metastatic gastric cancer. *Anticancer Res* 2011; **31**: 3543-3554 [PMID: 21965776]

7 **Cervantes A**, Roda D, Tarazona N, Roselló S, Pérez-Fidalgo JA. Current questions for the treatment of advanced gastric cancer. *Cancer Treat Rev* 2013; **39**: 60-67 [PMID: 23102520]

8 **Shen DW**, Pouliot LM, Hall MD, Gottesman MM. Cisplatin resistance: a cellular self-defense mechanism resulting from multiple epigenetic and genetic changes. *Pharmacol Rev* 2012; **64**: 706-721 [PMID: 22659329]

9 **Chen WW**, Wang F, Xu RH. Platinum-based versus non-platinum-based chemotherapy as first line treatment of inoperable, advanced gastric adenocarcinoma: a meta-analysis. *PLoS One* 2013; **8**: e68974 [PMID: 23874831 DOI: 10.1371/journal.pone.0068974]

10 **Koizumi W**, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215-221 [PMID: 18282805]

11 **Cunningham D**, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 36-46 [PMID: 18172173 DOI: 10.1056/NEJMoa073149]

12 **Kang YK**, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, Philco-Salas M, Suarez T, Santamaria J, Forster G, McCloud PI. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009; **20**: 666-673 [PMID: 19153121]

13 **Fujii M**, Kochi M, Takayama T. Recent advances in chemotherapy for advanced gastric cancer in Japan. *Surg Today* 2010; **40**: 295-300 [PMID: 20339982 DOI: 10.1007/s00595-009-4148-9]

14 **Machover D**, Goldschmidt E, Chollet P, Metzger G, Zittoun J, Marquet J, Vandenbulcke JM, Misset JL, Schwarzenberg L, Fourtillan JB. Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol* 1986; **4**: 685-696 [PMID: 3517242]

15 **Kok TC**, van der Gaast A, Splinter TA. 5-fluorouracil and folinic acid in advanced adenocarcinoma of the esophagus or esophago-gastric junction area. Rotterdam Esophageal Tumor Study Group. *Ann Oncol* 1996; **7**: 533-534 [PMID: 8839912]

16 **Barone C**, Corsi DC, Pozzo C, Cassano A, Fontana T, Noviello MR, Landriscina M, Colloca G, Astone A. Treatment of patients with advanced gastric carcinoma with a 5-fluorouracil-based or a cisplatin-based regimen: two parallel randomized phase II studies. *Cancer* 1998; **82**: 1460-1467 [PMID: 9554521]

17 **Cullinan SA**, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, Windschitl HE, Twito DI, Marschke RF, Foley JF. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. *JAMA* 1985; **253**: 2061-2067 [PMID: 2579257]

18 **Boku N**, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Takiuchi H, Nasu J, Ohtsu A. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncol* 2009; **10**: 1063-1069 [PMID: 19818685]

19 **Ohtsu A**, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H, Yoshida S. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003; **21**: 54-59 [PMID: 12506170]

20 **Blum M**, Suzuki A, Ajani JA. A comprehensive review of S-1 in the treatment of advanced gastric adenocarcinoma. *Future Oncol* 2011; **7**: 715-726 [PMID: 21675835 DOI: 10.2217/fon.11.50]

21 **Ma Y**, Tang L, Wang HX, Xu YC, Ma Y, Zhang FC. Capecitabine for the treatment for advanced gastric cancer: efficacy, safety and ethnicity. *J Clin Pharm Ther* 2012; **37**: 266-275 [PMID: 21950464 DOI: 10.1111/j.1365-2710.2011.01289.x]

22 **Ajani J**. Review of capecitabine as oral treatment of gastric, gastroesophageal, and esophageal cancers. *Cancer* 2006; **107**: 221-231 [PMID: 16770784 DOI: 10.1002/cncr.21986]

23 **Hong YS**, Song SY, Lee SI, Chung HC, Choi SH, Noh SH, Park JN, Han JY, Kang JH, Lee KS, Cho JY. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. *Ann Oncol* 2004; **15**: 1344-1347 [PMID: 15319239]

24 **Koizumi W**, Saigenji K, Ujiie S, Terashima M, Sakata Y, Taguchi T. A pilot phase II study of capecitabine in advanced or recurrent gastric cancer. *Oncology* 2003; **64**: 232-236 [PMID: 12697963]

25 **Jeung HC**, Rha SY, Shin SJ, Ahn JB, Noh SH, Roh JK, Chung HC. A phase II study of S-1 monotherapy administered for 2 weeks of a 3-week cycle in advanced gastric cancer patients with poor performance status. *Br J Cancer* 2007; **97**: 458-463 [PMID: 17653073]

26 **Lee JL**, Kang YK, Kang HJ, Lee KH, Zang DY, Ryoo BY, Kim JG, Park SR, Kang WK, Shin DB, Ryu MH, Chang HM, Kim TW, Baek JH, Min YJ. A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. *Br J Cancer* 2008; **99**: 584-590 [PMID: 18665164]

27 **Nishiyama M**, Wada S. Docetaxel: its role in current and future treatments for advanced gastric cancer. *Gastric Cancer* 2009; **12**: 132-141 [PMID: 19890692 DOI: 10.1007/s10120-009-0521-z]

28 **Sakamoto J**, Matsui T, Kodera Y. Paclitaxel chemotherapy for the treatment of gastric cancer. *Gastric Cancer* 2009; **12**: 69-78 [PMID: 19562460 DOI: 10.1007/s10120-009-0505-z]

29 **Ajani JA**, Fairweather J, Dumas P, Patt YZ, Pazdur R, Mansfield PF. Phase II study of Taxol in patients with advanced gastric carcinoma. *Cancer J Sci Am* 1998; **4**: 269-274 [PMID: 9689986]

30 **Emi Y**, Yamamoto M, Takahashi I, Orita H, Kakeji Y, Kohnoe S, Maehara Y. Phase II study of weekly paclitaxel by one-hour infusion for advanced gastric cancer. *Surg Today* 2008; **38**: 1013-1020 [PMID: 18958560 DOI: 10.1007/s00595-008-3769-8]

31 **Roth AD**, Ajani J. Docetaxel-based chemotherapy in the treatment of gastric cancer. *Ann Oncol* 2003; **14** Suppl 2: ii41-ii44 [PMID: 12810457]

32 **Bang YJ**, Kang WK, Kang YK, Kim HC, Jacques C, Zuber E, Daglish B, Boudraa Y, Kim WS, Heo DS, Kim NK. Docetaxel 75 mg/m(2) is active and well tolerated in patients with metastatic or recurrent gastric cancer: a phase II trial. *Jpn J Clin Oncol* 2002; **32**: 248-254 [PMID: 12324575]

33 **Sulkes A**, Smyth J, Sessa C, Dirix LY, Vermorken JB, Kaye S, Wanders J, Franklin H, LeBail N, Verweij J. Docetaxel (Taxotere) in advanced gastric cancer: results of a phase II clinical trial. EORTC Early Clinical Trials Group. *Br J Cancer* 1994; **70**: 380-383 [PMID: 7914428]

34 **Farhat FS**. A general review of the role of irinotecan (CPT11) in the treatment of gastric cancer. *Med Oncol* 2007; **24**: 137-146 [PMID: 17848736]

35 **Enzinger PC**, Kulke MH, Clark JW, Ryan DP, Kim H, Earle CC, Vincitore MM, Michelini AL, Mayer RJ, Fuchs CS. A phase II trial of irinotecan in patients with previously untreated advanced esophageal and gastric adenocarcinoma. *Dig Dis Sci* 2005; **50**: 2218-2223 [PMID: 16416165 DOI: 10.1007/s10620-005-3038-2]

36 **Köhne CH**, Catane R, Klein B, Ducreux M, Thuss-Patience P, Niederle N, Gips M, Preusser P, Knuth A, Clemens M, Bugat R, Figer I, Shani A, Fages B, Di Betta D, Jacques C, Wilke HJ. Irinotecan is active in chemonaive patients with metastatic gastric cancer: a phase II multicentric trial. *Br J Cancer* 2003; **89**: 997-1001 [PMID: 12966415]

37 **Vanhoefer U**, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E, Planker M, Santos JG, Piedbois P, Paillot B, Bodenstein H, Schmoll HJ, Bleiberg H, Nordlinger B, Couvreur ML, Baron B, Wils JA. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: A trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000; **18**: 2648-2657 [PMID: 10894863]

38 **Webb A**, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997; **15**: 261-267 [PMID: 8996151]

39 **Wils JA**, Klein HO, Wagener DJ, Bleiberg H, Reis H, Korsten F, Conroy T, Fickers M, Leyvraz S, Buyse M. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin--a step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 1991; **9**: 827-831 [PMID: 2016625]

40 **Cao S**, Durrani FA, Rustum YM. Synergistic antitumor activity of capecitabine in combination with irinotecan. *Clin Colorectal Cancer* 2005; **4**: 336-343 [PMID: 15663838]

41 **Fujimoto-Ouchi K**, Tanaka Y, Tominaga T. Schedule dependency of antitumor activity in combination therapy with capecitabine/5'-deoxy-5-fluorouridine and docetaxel in breast cancer models. *Clin Cancer Res* 2001; **7**: 1079-1086 [PMID: 11309360]

42 **Wada Y**, Yoshida K, Suzuki T, Mizuiri H, Konishi K, Ukon K, Tanabe K, Sakata Y, Fukushima M. Synergistic effects of docetaxel and S-1 by modulating the expression of metabolic enzymes of 5-fluorouracil in human gastric cancer cell lines. *Int J Cancer* 2006; **119**: 783-791 [PMID: 16557585 DOI: 10.1002/ijc.21879]

43 **Luo HY**, Wang ZQ, Wang FH, Qiu MZ, Teng KY, Ruan DY, He YJ, Li YH, Xu RH. Phase 2 study of capecitabine and irinotecan combination chemotherapy (modified XELIRI regimen) in patients with advanced gastric cancer. *Am J Clin Oncol* 2011; **34**: 555-560 [PMID: 22101386 DOI: 10.1097/COC.0b013e3181f47ac1]

44 **Mochiki E**, Ogata K, Ohno T, Toyomasu Y, Haga N, Fukai Y, Aihara R, Ando H, Uchida N, Asao T, Kuwano H. Phase II multi-institutional prospective randomised trial comparing S-1+paclitaxel with S-1+cisplatin in patients with unresectable and/or recurrent advanced gastric cancer. *Br J Cancer* 2012; **107**: 31-36 [PMID: 22617130]

45 **Mochiki E**, Ohno T, Kamiyama Y, Aihara R, Haga N, Ojima H, Nakamura J, Ohsawa H, Nakabayashi T, Takeuchi K, Asao T, Kuwano H. Phase I/II study of S-1 combined with paclitaxel in patients with unresectable and/or recurrent advanced gastric cancer. *Br J Cancer* 2006; **95**: 1642-1647 [PMID: 17133268]

46 **Moehler M**, Kanzler S, Geissler M, Raedle J, Ebert MP, Daum S, Flieger D, Seufferlein T, Galle PR, Hoehler T. A randomized multicenter phase II study comparing capecitabine with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2010; **21**: 71-77 [PMID: 19605504]

47 **Murad AM**, Petroianu A, Guimaraes RC, Aragao BC, Cabral LO, Scalabrini-Neto AO. Phase II trial of the combination of paclitaxel and 5-fluorouracil in the treatment of advanced gastric cancer: a novel, safe, and effective regimen. *Am J Clin Oncol* 1999; **22**: 580-586 [PMID: 10597742]

48 **Narahara H**, Iishi H, Imamura H, Tsuburaya A, Chin K, Imamoto H, Esaki T, Furukawa H, Hamada C, Sakata Y. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer* 2011; **14**: 72-80 [PMID: 21340666 DOI: 10.1007/s10120-011-0009-5]

49 **Oh SC**, Sur HY, Sung HJ, Choi IK, Park SS, Seo JH, Jeen YT, Chun HJ, Shin SW, Mok YJ, Kim JS, Kim YH. A phase II study of biweekly dose-intensified oral capecitabine plus irinotecan (bXELIRI) for patients with advanced or metastatic gastric cancer. *Br J Cancer* 2007; **96**: 1514-1519 [PMID: 17473829]

50 **Park SH**, Lee WK, Chung M, Lee Y, Han SH, Bang SM, Cho EK, Shin DB, Lee JH. Paclitaxel versus docetaxel for advanced gastric cancer: a randomized phase II trial in combination with infusional 5-fluorouracil. *Anticancer Drugs* 2006; **17**: 225-229 [PMID: 16428942]

51 **Pozzo C**, Barone C, Szanto J, Padi E, Peschel C, Bükki J, Gorbunova V, Valvere V, Zaluski J, Biakhov M, Zuber E, Jacques C, Bugat R. Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study. *Ann Oncol* 2004; **15**: 1773-1781 [PMID: 15550582]

52 **Ueda Y**, Yamagishi H, Ichikawa D, Okamoto K, Otsuji E, Morii J, Koizumi K, Kakihara N, Shimotsuma M, Yamashita T, Taniguchi F, Aragane H, Nishi H, Itokawa Y, Morita S, Sakamoto J. Multicenter phase II study of weekly paclitaxel plus S-1 combination chemotherapy in patients with advanced gastric cancer. *Gastric Cancer* 2010; **13**: 149-154 [PMID: 20820983 DOI: 10.1007/s10120-010-0548-1]

53 **Yeh KH**, Lu YS, Hsu CH, Lin JF, Hsu C, Kuo SH, Li SJ, Cheng AL. Phase II study of weekly paclitaxel and 24-hour infusion of high-dose 5-fluorouracil and leucovorin in the treatment of recurrent or metastatic gastric cancer. *Oncology* 2005; **69**: 88-95 [PMID: 16088236]

54 **Jeung HC**, Rha SY, Im CK, Shin SJ, Ahn JB, Yang WI, Roh JK, Noh SH, Chung HC. A randomized phase 2 study of docetaxel and S-1 versus docetaxel and cisplatin in advanced gastric cancer with an evaluation of SPARC expression for personalized therapy. *Cancer* 2011; **117**: 2050-2057 [PMID: 21523716 DOI: 10.1002/cncr.25729]

55 **Baek JH**, Kim JG, Jeon SB, Chae YS, Kim DH, Sohn SK, Lee KB, Choi YJ, Shin HJ, Chung JS, Cho GJ, Jung HY, Yu W. Phase II study of capecitabine and irinotecan combination chemotherapy in patients with advanced gastric cancer. *Br J Cancer* 2006; **94**: 1407-1411 [PMID: 16641916]

56 **Jatoi A**, Tirona MT, Cha SS, Alberts SR, Rowland KM, Morton RF, Nair S, Kardinal CG, Stella PJ, Mailliard JA, Sargen D, Goldberg RM. A phase II trial of docetaxel and CPT-11 in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction, and gastric cardia. *Int J Gastrointest Cancer* 2002; **32**: 115-123 [PMID: 12794247]

57 **Bouché O**, Raoul JL, Bonnetain F, Giovannini M, Etienne PL, Lledo G, Arsène D, Paitel JF, Guérin-Meyer V, Mitry E, Buecher B, Kaminsky MC, Seitz JF, Rougier P, Bedenne L, Milan C. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD 9803. *J Clin Oncol* 2004; **22**: 4319-4328 [PMID: 15514373]

58 **Dank M**, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C, Wenczl M, Goker E, Cisar L, Wang K, Bugat R. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2008; **19**: 1450-1457 [PMID: 18558665]

59 **Kim JG**, Sohn SK, Kim DH, Baek JH, Sung WJ, Park JY, Kim TB, Jung HY, Yu W, Lee KB. Phase II study of docetaxel and capecitabine in patients with metastatic or recurrent gastric cancer. *Oncology* 2005; **68**: 190-195 [PMID: 16006756]

60 **Giordano KF**, Jatoi A, Stella PJ, Foster N, Tschetter LK, Alberts SR, Dakhil SR, Mailliard JA, Flynn PJ, Nikcevich DA. Docetaxel and capecitabine in patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction: a phase II study from the North Central Cancer Treatment Group. *Ann Oncol* 2006; **17**: 652-656 [PMID: 16497828]

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**Table 1 Selected phase II and III trials of first-line non-platinum-based chemotherapy for patients with advanced gastric cancer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Year** | **Phase** | **Tx** | **Dose (mg/m2 per day)** | **Cycle** | **Patients (*n*)** | **RR**  | **Median TTP/TTF/PFS (mo)** | **Median OS (mo)** | ***P*-value for OS** |
| Vanhoefer *et al*[[34](#_ENREF_34)] | 2000 | III | FAMFCELF | (5FU: 1500, A: 30, M: 1500)(F: 1000, C: 100)(L: 300, E: 120, F: 500) | (D1, D1, and D15, 4 wk)(D1-5 and D2, 4 wk)(D1-5, 3wks) | 858179 | 12%20%9% | 3.34.13.3 | 6.77.27.2 | -0.770.73 |
| Boku *et al*[[15](#_ENREF_15)] | 2009 | III | FICS | F: 800(I: 70, C: 80)S: 80 | D1-5, 4 wk(D1,15 and D1, 4 wk)D1-28, 6 wk | 234236234 | --- | 2.94.84.2 | 10.812.311.4 | -0.0551< 0.0012 |
| Ohtsu *et al*[[16](#_ENREF_16)] (JCOG 9205)  | 2003 | III | FFCU/T3 | F: 800(F: 800, C: 20)C/T: 750 | D1-5, 4 wk(D1-5 and D1-5, 4 wk)- | 10510570 | 11.4%34.3%8.6% | 1.93.92.4 | 7.17.66.0 | -0.340.11 |
| Kim *et al*[[57](#_ENREF_57)] | 2005 | II | DX | D: 75X: 2000 | D1, 3 wkD1-14, 3 wk | 32 | 43.8% | 5.1 | 8.4 | - |
| Giordano *et al*[[58](#_ENREF_58)] (NCCTG)  | 2006 | II | DX | D: 75X: 1650 | D1, 3 wkD1, 3 wk | 44 | 39% | 4.2 | 9.4 | - |
| Jeung *et al*[[52](#_ENREF_52)] | 2011 | II (random) | DSDC | (D: 35, S: 70)(D: 35, C: 35) | (D1, 8 and D1-14, 3 wk)(D1, 8 and D1, 8, 3 wk) | 3941 | 46%24% | 7.34.8 | 16.08.2 | 0.019 |
| Park *et al*[[48](#_ENREF_48)] | 2006 | II (random) | PFDF | (P: 175, F: 500)(D: 75, F: 500) | (D1 and D1-5, 3 wk)(D1 and D1-5, 3 wk) | 3839 | 42%33% | 3.64.2 | 9.99.3 | - |
| Mochiki *et al*[[42](#_ENREF_42)]  | 2012 | II (random) | SPSC | (S: 80, P: 60)(S: 80, C: 60) | (D1-14 and D1, 8, 15, 4 wk)(D1-21 and D8, 5 wk) | 4241 | 52.3%48.7% | 9.06.0 | 16.017.0 | 0.084 |
| Pozzo *et al*[[49](#_ENREF_49)] | 2004 | II (random) | ILFIC | (I: 80, L:500, F: 2000)(I: 200, C: 60) | (D1, weekly, 6 wk)(D1 and D1, 3 wk) | 7472 | 42.4%32.1% | 6.54.2 | 10.76.9 | 0.0018 |
| Narahara *et al*[[46](#_ENREF_46)] (GC0301/TOP-002)  | 2011 | III | ISS | (S: 80, I: 80)S: 80 | (D1-21, 5 wk,D1 and 15, 5 wk)D1-28, 6 wk | 164162 | 41.5%26.9% | 4.53.6 | 12.810.5 | 0.233 |
| Moehler *et al*[[44](#_ENREF_44)]  | 2010 | II (random) | IXCX | (I: 250, X: 2000)(C: 80, X: 2000) | (D1 and D1-14, 3 wk)(D1 and D1-14, 3 wk) | 5755 | 37.7%42.0% | 4.24.8 | 10.27.9 | - |
| Oh *et al*[[47](#_ENREF_47)] | 2007 | II | IX | (I: 130, X: 3500) | (D1,15 and D1-15, 3 wk) | 55 | 43.6% | 5.0 | 11 | - |
| Baek *et al*[[53](#_ENREF_53)] | 2006 | II | IX | (I:100, X:2000) | (D1, 8 and D1-14, 3 wk) | 41 | 46.3% | 5.1 | 8.6 | - |
| Bouche *et al*[[55](#_ENREF_55)] (FFCD 9803)  | 2004 | II | LFLFCLFI | (L: 200, F: 400/600)(L: 200, F: 400/600, C: 50)(F: 200, F: 400/600, I: 180) | (D1-2, 2 wk)(D1-2, 2 wk)(D1-2, 2 wk) | 454445 | 13%27%40% | 3.24.96.9 | 6.89.511.3 | - |
| Dank *et al*[[56](#_ENREF_56)]  | 2008 | III | IFLCF | (I: 80, L: 500, F: 2000)(C:100, F:1000) | (D1, weekly, 6 wk)(D1 and D1-5, 4 wk) | 172165 | 31.8%25.8% | 5.04.2 | 9.08.7 | 0.53 |

1Superiority compared to 5-fluorouracil (5FU) alone; 2Non-inferiority compared to 5FU alone; 3With weekly bolus infusion of mitomycin 5 mg/m2. Tx: Treatment; TTP: Time to progression; TTF: Time to treatment failure; PFS: Progression-free survival; OS: Overall survival; F: 5FU; A: Adriamycin; M: Methotrexate; C: Cisplatin; E: Etoposide; L: Leucovorin; I: Irinotecan; S: S-1; U/T: Uracil and tegafur; D: Docetaxel; X: Capecitabine; NCCTG: P: Paclitaxel.