



Comparative Study between Anthracycline Based Regimen and Taxane Based Regimen in Metastatic Gastric Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Author AI designed the study, wrote the protocol, followed up the patients, performed the statistical analysis and wrote the first draft of the manuscript. Author MAS did the surgical part and followed up the patients after surgery and managed the analyses of the study with all authors. Author AH collected the data, followed up the patients and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Taxanes and anthracycline containing regimes are the most successful regimens in advanced gastric cancer with comparable results but with different toxicity profiles.

Objective: To compare efficacy and toxicity of 2 regimens one containing anthracycline (ECSF regimen) and other contain taxane (PCF regimen) as a first line therapy in advanced gastric cancer.

Methods: Between May 2011 and Dec 2015, a total of 120 patients with locally advanced and metastatic gastric adenocarcinoma were included in the study, 60 patients received ECSF (Epirubicin 50 mg/m² iv d1, Cisplatin 60 mg/m² iv d1, 5-FU 1750 mg/m²/d "1 and 8" CIVI over 24 h, Folinic acid 200 mg /m² day 1, 8 repeated every 3 weeks), while, another 60 patients received PCF (Paclitaxel 150 mg/m² IV on day 1; Cisplatin 15 mg/m² IV on days 1-5 and 5-FU 600mg/m²/day

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CIVI d1-5 every 3 weeks) until disease progression or unacceptable toxicities.

Results: ORR of ECSF was superior to PCF arm, 47% vs. 34% respectively $p = 0.001$. The toxicity profiles were less in ECSF arm than PCF arm especially in neutropenia and mucositis. Median PFS and OS were significantly higher in ECSF arm than PCF (6.9 vs. 4.9 months $p = 0.022$) and (11.1 vs.8.9 months $p = 0.028$) respectively.

Conclusion: The use of anthracycline based regimen as first line therapy in advanced gastric cancer showed better outcome and acceptable toxicity when it compared with paclitaxel containing regimen.

Keywords: Modified ECF; gastric cancer; Taxanes based regimen.

1. INTRODUCTION

Gastric cancer is one of the leading causes of cancer death worldwide [1]. Epirubicin, cisplatin and continuous infusional 5-fluorouracil (ECF) is a well-established regimen for treatment of Advanced Gastric Cancer (AGC) [2,3]. The administration of ECF requires the use of an ambulatory infusion device however, many institutions especially in developing countries can't provide this service. So various schedules of 5-FU administration have been studied, one of them is co-administration of the modulator folinic acid [4]. One of EORTC trials compared 5-FU alone with 5-FU plus folinic acid. They found the addition of folinic acid enhanced the response rate and prolonged the time to disease progression, without increasing toxicity [5] Recent study by Karapetis C et al. [6]; showed ECF, Epirubicin, Cisplatin and 5-FU using dose 1750 mg/m² day 1,8 and sodium folinic acid showed similar results to standard ECF.

On the other hand, Taxanes (paclitaxel and docetaxel) have been studied in (AGC) as a single agent or combination [7-10]. A large randomized phase III study showed increased efficacy with the combination of docetaxel, cisplatin and 5-FU (DCF). However, the toxicity profile of regimen (up to 82% of grade 3/4 hematological toxicity) made it hard to apply in clinical practice [11]. Since paclitaxel and docetaxel have similar anticancer activity in AGC with different toxicity profile, several studies used paclitaxel in advanced gastric cancer and it showed promising results [12].

As most guideline recommend anthracycline based or taxanes based regimen as first line metastatic [13,14]. We designed this study to compare two regimens with convenient doses of administration and low cost, one containing anthracycline ECSF regimen [6] and other

contain paclitaxel PCF regimen [15]. On our patients to determine their efficacy and their affection on progression free survival and overall survival, As they both have been studied separately and they showed comparable results to each other and to the standard regimens.

2. PATIENTS AND METHODS

2.1 Patients

Patients selection for each regimen was done randomly. All patients were included if they met the following eligibility criteria: histologically proven gastric adenocarcinoma, non-operable locally advanced, or metastatic disease or relapsed disease after initial resection but with measurable or assessable lesions; Patients were ≥ 18 years old, Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or less, no prior chemotherapy, adequate function of bone marrow hemoglobin ≥ 9.5 g/dL, white blood cell (WBC) count $\geq 4.0 \times 10^9/L$, neutrophil count $\geq 2.0 \times 10^9/L$, and platelets $\geq 100.0 \times 10^9/L$. heart (cardiac ejection fraction within normal limits), kidneys (creatinine $\leq 1.0 \times$ UNL), and liver (Total bilirubin $\leq 1.0 \times$ UNL aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ UNL (AST and ALT $\leq 5 \times$ UNL in patients with hepatic metastasis). None of the following criteria were permitted: previous chemotherapy, patients allergic to taxanes, preexisting peripheral neuropathy second malignancy, uncontrolled infection, symptomatic CNS metastases, (parallel radiation therapy, other parallel therapy aiming at tumor reduction, and life expectancy of less than 3 months. All patients signed informed consent.

The study was approved by the institutional review board, in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

2.2 Pretreatment Evaluation

All patients have subjected to full history taken, body examination, and recoding of all tumor-related symptoms. A blood samples was collected for CBC, multichannel chemical surveys, and electrolyte measurements. The following investigations were performed obligatorily at study entry: ECG, echocardiogram with evaluation of ventricular function, measurement of the creatinine clearance, audiogram, chest x-ray, abdominal ultrasound, computed tomography (CT) of the abdomen, and, only if indicated, CT scan of the thorax, and gastroscopy (if indicated).

2.3 Methods

It is a prospective study. The patients were randomized into 2 groups (group-1) included 60 patients received ECSF regimen [6].(Epirubicin 50 mg/m² and Cisplatin 60 mg/m² given on day 1, with 5-FU (1750mg/m² administered as 24-hour infusion on day 1 and day 8 and sodium Folate (200 mg/m²) IV push every 21 days cycle). Cisplatin was administered with standard hydration regimen, including potassium and magnesium salt supplementation. Standard antiemetic medication was used, including dexamethasone and a 5HT3 antagonist.

Group -2 included 60 patients received (PCF) [15,16] Paclitaxel 150 mg/m² IV, D1 Cisplatin 15 mg/m² IV, D1-5 , 5-FU 600mg/m²/d CIVI D1-5, Every "3 weeks".

All patients in PCF regimen received standard intravenous hypersensitivity prophylaxis, including dexamethasone 10 mg, cimetidine 300 mg and diphenhydramine 40 mg, 30 min before administration of paclitaxel.

Chemotherapy was administered until tumor progression, side effects, or a maximum of 8 cycles. Assessment of tumor related symptoms was performed every 3 weeks. Evaluation of side effects took place on a weekly basis.

2.4 Adverse Effects and Dose Modification

Toxicity was reported by using a National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0 [17]. If hematological toxicity \geq grade 3, grade 3 diarrhea lasting for more than 7 d despite the administration of loperamide, grade

3-4 mucositis lasting for more than 5 d and peripheral neuropathy \geq grade 2 occurred during the previous cycle, the daily dose of 5-FU or paclitaxel decreased by 20%. Chemotherapy of the next cycle started only after all the adverse effects recovered to grade 0-1 as judged according to NCI-CTG classification criteria. Dose escalation after dose reduction was not permitted. Granulocyte colony stimulating factor (G-CSF) was given if the neutropenia \geq grade 3 after chemotherapy.

2.5 Assessment and Statistics

Response was evaluated every three cycles of treatment by using Response Evaluation Criteria in Solid Tumors (RECIST). Complete response (CR) was defined as complete disappearance of all evaluable lesions, persisting for >4 weeks.

Partial response (PR) was defined as a \geq 30% reduction in the sum of the products of the largest perpendicular diameters in all measurable lesions for \geq 4 weeks, without the development of new lesions. Progressive Disease (PD) was defined as an increase in a previous lesion by >20%, or the development of any new lesion. Stable disease (SD) was defined as any change in a previous lesion that did not fit into either the PR or PD categories. The primary endpoint was overall survival (OS), and secondary endpoints were progression-free survival (PFS), response rate (RR) and toxicity. Survival time was analyzed by software Kaplan-Meier [18]. SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used.

3. RESULTS

3.1 Characteristics of Patients

Between May 2011 and December 2015, a total 120 patients were enrolled in the study. All patients had a histologically proven adenocarcinoma originating from the stomach. Their baseline characteristics are shown in (Table 1). Among them, 63 were male and 57 female with median age of 51 years (range, 32-62 years). 100 patients had ECOG performance status (PS) score 1 and 20 patients had ECOG PS 2. 60 patients were treated with ECSF therapy and 60 patients were treated with PCF therapy. In ECSF group 12 (20%) of them had locally advanced tumors while 48 (80%) had metastatic tumors. In PCF arm 15 patients (25%) had locally advanced tumor and 45 (75%)

patients had metastatic tumors. The total number of 242 cycles was delivered for ECSF, and 234 cycles for PCF. The median number of treatment cycles was four cycles (range, 2-8 cycles).

3.2 Efficacy

101 (84%) out of 120 patients were assessable for response. the tumor evaluation could not be performed in 19 patients. 8 patients in the ECSF arm refused further therapy (3 patients after one cycle and 5 patients after two cycles) because of toxicity whereas, in PCF arm 11 patients refused further therapy, 3 patients after one cycle and 4 after two cycles due to sever mucositis, one patients refused treatment after one cycle due peripheral neuropathy, one patient refused treatment due grade 4 neutropenia which needed admission to intermediate care unit and 2 patients missed after 2 cycles due to unknown cause.

The response rate of two regimens is shown in (Table 2). In 52 patients who were available for response in ECSF arm, no one achieved complete response, 24 patients had PR 47% (95% CI: 21.7-53.5%), 12 (24%) patients had SD and 16 (29%) didn't respond and their disease progressed on treatment. The disease control rate (PR+SD) was 71%.

In 49 patients in PCF who were eligible for assessment of response, no one has achieved CR, 17 (34%) patients had PR, 12 (24.5%) patients had SD and 20 (41.5%) patients had disease progression on treatment. The disease control rate (PR+SD) in PCF arm was 58.5%.

3.3 Toxicity

All patients were assessable for toxicity (Table 3). Regarding ECSF regimen, nausea and vomiting were more common than PCF arm but they were tolerable, however grade 3-4 hematotoxicity particularly anemia grade III-IV occurred in 33% of cycles and neutropenia grade III-IV occurred in 30% of cycles which lead to delay cycles in 15% of next cycles and dose reduction in 12% of next cycle. Growth factor was given in (27%) patients.

On the other hand, the most significant side effect in the PCF arm was neutropenia grade IV occurred in 40% which resulted into dose reduction of paclitaxel to 150 mg/m² in 25% of next cycles and use of growth factor in 17% of

next cycles, mucosities grade 4 occurred in (25%) of cycles which lead to 2 toxic death, asthenia, myalgia 10% and joint pain 15% and sensory neuropathy 6% which are more significant in this regimen than ECSF arm.

Table 1. Patients characteristics

Characteristics	PCF (N=60)	ECSF (N=60)
Gender	32(54.%)	31(52%)
Male	28(46%)	29 (48%)
Female		
Age	52	50
EGOC PS 1	48(80%)	52(88%)
2	12(20%)	8(12%)
Disease Status		
locally advanced	12(20%)	15(25%)
Metastatic	48(80%)	45 (75%)
Site of metastases		
liver	24	21
peritoneum	14	12
para-ortic LN	9	13
Bone	1	2
No of metastatic site	N=48	N=47
1	34(57%)	25(54%)
2	19(32%)	16(33%)
3	6(10%)	7(12%)

ECOG PS: Eastern Cooperative Oncology Group performance status, LN: lymph node

Table 2. Response rate in assessed patients

	PCF n= 49	ECSF n=52	P- Value
CR	0(0%)	0(0%)	NS
PR	17(34%)	25(47%)	P=0.04
SD	12(24%)	13(24%)	NS
PD	20(41%)	14(28%)	P=0.001

3.4 Surgery

27 patients with locally advanced stomach received chemotherapy (12 patients in ECSF arm and 15 patients in PCF arm. resection was not possible and the only procedure which could be done was purely for palliation of symptoms in the form of gastrojejunostomy enteroentrostomy or feeding jejunostomy. After median 5 cycles of chemotherapy, one patient had attempted resection of their tumor in PCF arm, but histological examination revealed that excision margin is infiltrated. A complete resection with free margin was performed in 3 patients in the ECSF arm where total gastrectomy with D2 resection and Roux- en Y reconstruction was done. Also resection of infiltrated transverse

colon and re-anastomosis in one patient was performed.

3.5 Survival

The median time to tumor progression in the ECSF arm was 6.9 months (95% CI, 4.8 to 9.7 months), and in the PCF arm, it was 4.9 months (95% CI, 3.0 to 7.1 months $p=0.002$); (Fig. 1).

The median overall survival time for patients treated with ECSF and PCF was 11.1 months (95% CI, 6.3 to 15.5 months) and 8.9 months (95% CI, 5.1 to 10.8 months $p=0.028$); (Fig. 2), respectively.

3.6 Quality of Life

43 patients in the ECSF arm and 46 patients in the PCF arm had tumor-related symptoms before therapy. 26 out of 43 patients 61% (95% CI 50% - 75%) treated with ECSF and 21/49 patients 45% (95% CI, 42% - 72%) treated with PCF showed an improvement in at least one of their symptoms without worsening of any other symptoms.

4. DISCUSSION

Our data showed that anthracyclin regimen (ECSF) has superior results when compared with Taxan regimen (PCF) with ORR of 47% vs. 34% respectively. Furthermore, toxicity profiles were more tolerable in ECSF arm than PCF arm, grade 3 to 4 neutropenia occurred in (30%) of ECSF cycles but not resulted in any toxic death, that due to using of growth factors and reduction of the dose of 20% 5FU if leukopenia persists on the following cycle. On the other hand, the toxicity profiles of PCF were higher the most prominent were neutropenia 40% mucosites 30% which resulted in 2 toxic deaths.

The superiority of response ECSF arm also translated into significant higher median PFS than PCF arm (6.9 months (95% CI, 4.8 to 9.7months) vs. 4.9 months (95% CI, 3.0-7) $p=0.022$. And higher median OS of 11.1 months (95% CI, 6.3 to 15.5 months) vs.8.9 months (95% CI, 5.1 to 10.8) $p=0.028$.

The results of ECSF are comparable with the results of Karapetis et al. [6], who firstly used this regimen. Moreover, they were similar to earlier

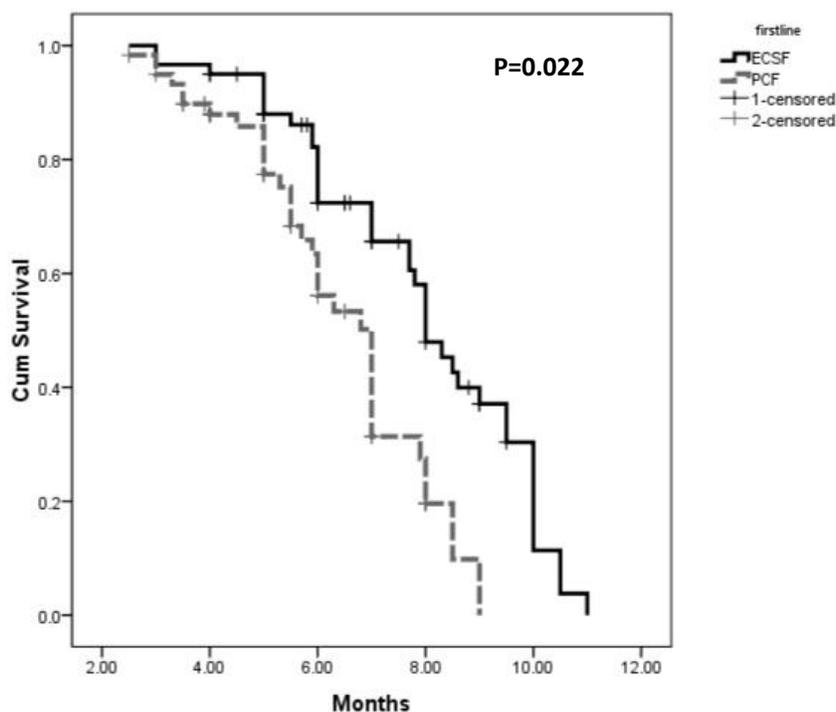


Fig. 1. Progression free survival difference between ECSF and PCF regimens

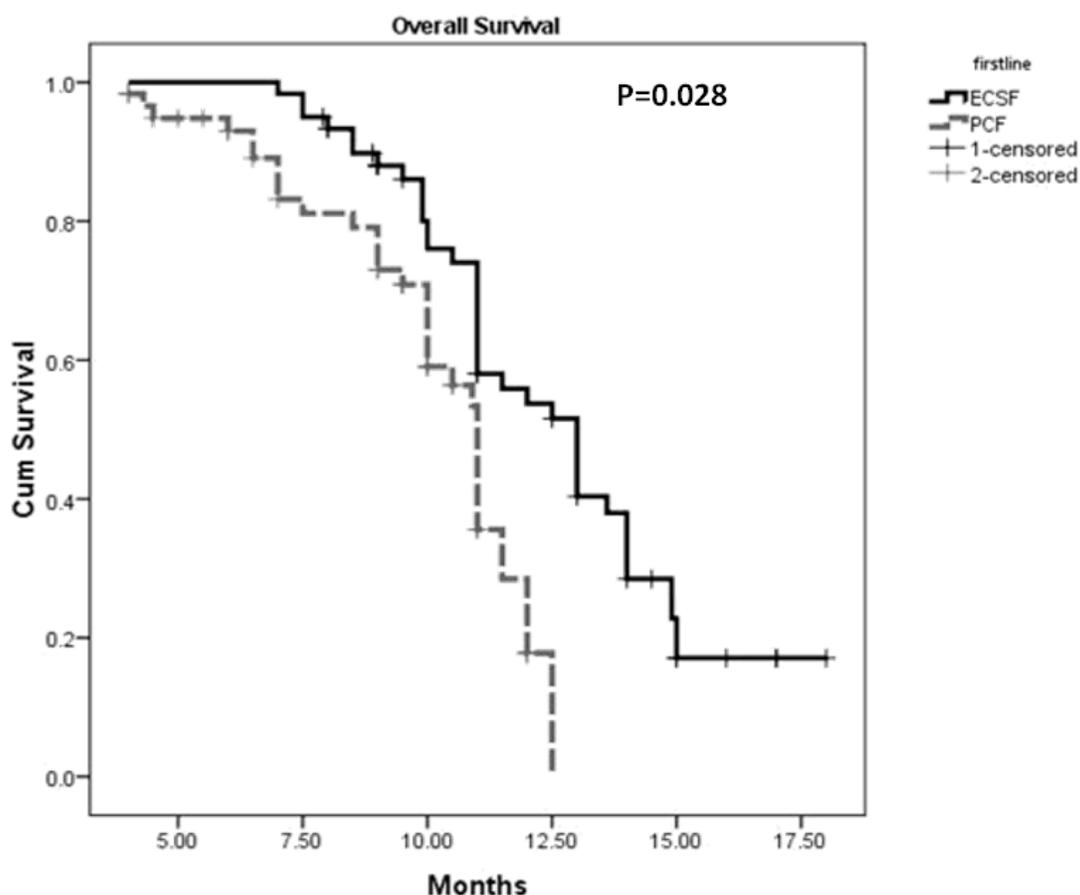


Fig. 2. Overall Survival difference between ECSF and PCF regimens

Table 3. Toxicity profiles of the 2 regimens

Adverse event	PCF		ECSF		p
	Grade 1-2	Grade3-4	Grade 1-2	Grade 3-4	
Anorexia	30%	2%	35%	3%	NS
Diarrhea	10%	2%	13%	0%	NS
Nausea	35%	5%	44%	10%	0.037
Vomiting	10%	0%	20%	4%	0.010
Fatigue	25%	5%	17%	4%	0.045
Neutropenia	30%	40%	40%	30%	0.039
Fever	8%	8%	10%	4%	0.045
Mucositis	30	25	25	15	0.023
Anemia	20%	10%	39%	33%	0.047
Liver impairment	10%	5%	8%	3%	NS
Sensory neuropathy	6%	0%	7%	0%	NS

results of ECF regimen which was done by Webbs et al. [19]. However, the hematological toxicity of ECSF was higher than hematological toxicity reported in the original work of ECF [20] (20% v 30%) possibly due to intensive dose on day 1&8 in ECSF regimen. PFS results of ECSF

are in line with original work of ECF who reported PFS 7.4 months while the OS was higher in our results 11.1 months compared to the earlier studies which was around 8.9 months [19,20] this could be explained by using the second and

third line of chemotherapy which might not be available to all patients in mid and late 1990.

Regarding the PCF arm ORR was 34% in our study which was inferior to the recent study by Zhang X et al. [15], who reported ORR 42%. The toxicity profiles were comparable with recent study but we reported high incidence of mucositis than Zhang et al. who reported 40% grade IV neutropenia but 0% grade IV mucositis, according to our experience in our patients we think it is impossible to get 0% of grade IV mucositis despite grade IV neutropenia occurred in 40%. Despite the PFS regimen was equivalent with the results of earlier study used this regimen and reported PFS of 4.2 months [21]. It was inferior to recent studies which used PCF and achieved PFS 5.7 months [15,21-23]. Also the OS 8.9 months was superior to results of early study which reported 6.4 months, but it was inferior to recent study of PCF which reported median 12 months OS [15,21-23].

Despite the limitation of our study by its small number of patients, we found great advantage of using ECSF regimen over PCF regimen regarding efficacy, the cost of therapy, fewer days of admission and tolerability and the latest NCCN guideline 2016 also support our data as they put ECF with its modifications as category one in regimens recommended to use as first line metastatic while the regimen which contain Taxane (docetaxel) they put it as category 2B [24].

5. CONCLUSION

Our results showed that use of anthracycline based regimen as first line therapy in advanced and metastatic gastric cancer in the form of (ECSF), has better outcome and acceptable toxicity when it compared with paclitaxel containing regimen (PCF) regimen and we also recommend its use as a neoadjuvant treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lee HJ, Yang HK and Ahn YO. Gastric cancer in Korea. *Gastric Cancer*. 2002;5: 177-182.
2. Andreyev HJ, Norman AR, Cunningham D, et al. Squamous oesophageal cancer can be downstaged using protracted venous infusion of 5-fluorouracil with epirubicin and cisplatin (ECF). *Eur J Cancer*. 1995; 31A:2209–14.
3. Cocconi G, DeLisi V, Di Blasio B. Randomized comparison of 5-FU alone or combined with mitomycin and cytarabine (MFC) in the treatment of advanced gastric cancer. *Cancer Treat Rep*. 1982;66:1263–6.
4. Machover D, Goldschmidt E, Chollet P, et al. Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol*. 1986;4:685–96.
5. Lutz MP, Wilke H, Wagener DJ, et al. Weekly infusional high-dose fluorouracil (HD-FU), HD-FU plus folinic acid (HD-FU/FA), or HD-FU/FA plus biweekly cisplatin in advanced gastric cancer: randomized phase II trial 40953 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group and the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol*. 2007; 25:2580–5.
6. Karapetis C, Cheong K, Yip D. A phase I and II trial of epirubicin, cisplatin, 24-hour infusion 5 fluorouracil and sodium folinate in patients with advanced esophagogastric carcinomas. *Asia-Pacific Journal of Clinical Oncology*. 2010;6:298–305.
7. Cascinu S, Graziano F, Cardarelli N, et al. Phase II study of paclitaxel in pretreated advanced gastric cancer. *Anticancer Drugs*. 1998;9:307-10.
8. Chao Y, Li CP, Chao TY, et al. An open, multi-centre, phase II clinical trial to evaluate the efficacy and safety of paclitaxel, UFT, and leucovorin in patients with advanced gastric cancer. *Br J Cancer*. 2006;95:159-63.
9. Einzig AI, Neuberg D, Remick SC, et al. Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: The Eastern Cooperative Oncology Group (ECOG) results of protocol E1293. *Med Oncol*. 1996;13:87-93.
10. Sakamoto J, Morita S, Yumiba T, et al. A phase II clinical trial to evaluate the effect of paclitaxel in patients with ascites caused by advanced or recurrent gastric carcinoma: A new concept of clinical

- benefit response for nonmeasurable type of gastric cancer. *Jpn J Clin Oncol*. 2003; 33:238-40.
11. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: A report of the V325 study group. *J Clin Oncol*. 2006;24:4991-7.
 12. Park SH, Lee WK, Chung M, et al. Paclitaxel versus docetaxel for advanced gastric cancer: A randomized phase II trial in combination with infusional 5-fluorouracil. *Anticancer Drugs*. 2006;17: 225-9.
 13. Thuss-Patience PC, Kretzschmar A, Repp M. Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: A randomized phase II study. *J Clin Oncol*. 2005;20;23(3):494-50.
 14. Teker F, Yilmaz B, Kemal Y, Kut E, Yucel I. Efficacy and safety of docetaxel or epirubicin, combined with cisplatin and fluorouracil, (DCF and ECF) regimens as first line chemotherapy for advanced gastric cancer: A retrospective analysis from Turkey. *Asian Pacific Journal of Cancer Prevention*. 2014;15(6):6727-32.
 15. Zhang X, Yongqian S, Zhang F, Liang J, Ma X, Chen L, Huang JJ, et al. Combination of paclitaxel, cisplatin, and fluorouracil in patients with advanced and metastatic gastric cancer as first- or second-line therapy: A multicenter prospective study. *J Clin Oncol*. 2011;29: (suppl; abstr e14561).
 16. Zhang X, Shu Y, Liang J. Combination chemotherapy with paclitaxel, cisplatin and fluorouracil for patients with advanced and metastatic gastric or esophagogastric junction adenocarcinoma: A multicenter prospective study. *Chin J Cancer Res*. 2012;24(4):291-298.
 17. National Cancer Institute. Cancer Therapy Evaluation Program, Common Toxicity Criteria. Version 2.0. Bethesda, MD: National Cancer Institute; 1999.
 18. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
 19. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol*. 1997;15(1):261-7.
 20. Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). *Ann Oncol*. 1994;5(7):609-16.
 21. Jung JY, Kwon JH, Kim JH, Song HH, Kim I, Lee KS, Kim HJ, Zang DY, Ahn JS, Lee JA, Park YI. Phase II study of the paclitaxel, cisplatin, 5-fluorouracil and leucovorin (TPFL) regimen in the treatment of advanced or metastatic gastric cancer. *Oncol Rep*. 2009;21(2):523-9.
 22. Takiuchi H, Goto M, Imamura H, et al. Multi-center phase II study for combination therapy with paclitaxel/ doxifluridine to treat advanced/recurrent gastric cancer showing resistance to S-1 (OGSG 0302). *Jpn J Clin Oncol*. 2008;38:176-81.
 23. Chon H, Rha S. Docetaxel versus paclitaxel combined with 5-FU and leucovorin in advanced gastric cancer: Combined analysis of two phase II trials. *Cancer Res Treat*. 2009;41(4):196-204.
 24. National Comprehensive Cancer Network Version 1; 2016.

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