EJMI

DOI: 10.14744/ejmi.2024.82171
EJMI 2024;8(4):238–244

Research Article

Capecitabine vs. 5-Fluorouracil: A Retrospective Study on Efficacy in Elderly Patients with Advanced Gastric Cancer

Yonca Yılmaz Ürün,[1] Berrak Mermit Erçek[2]

[1]Department of Gastroenterology and Hepatology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Türkiye
[2]Department of Medical Oncology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Türkiye

Abstract

Objectives: As the world population ages, the incidence of gastric cancer is increasing. This study aimed to compare the efficacy and adverse events of 5-Fluorouracil (5-FU)- and capecitabine-containing regimens in geriatric gastric cancer patients.

Methods: Our study included 258 geriatric patients with relapsed or metastatic gastric cancer at the time of diagnosis who were treated with 5-FU- or capecitabine-containing regimens in the oncology clinic of Van Yüzüncü Yıl University Faculty of Medicine between January 2006-December 2019. The patients were divided into two groups: patients receiving 5-FU-containing regimens and those receiving capecitabine-containing regimens. Medical records of the patients (demographical and clinical characteristics) were analyzed using appropriate statistical methods.

Results: A total of 258 patients (181 men and 77 women) were enrolled in the study. 96 patients were treated with capecitabine and 162 patients were treated with 5-FU-containing regimens. There was no statistically significant difference in median OS and PFS between the 5-FU and capecitabine groups (p>0,05). Grade 3-4 neutropenia, grade 3-4 anemia, grade 3-4 thrombocytopenia , and febrile neutropenia were more frequent in the 5-FU group (p<0.05).

Conclusion: Capecitabine was as effective as 5-FU. It is also more tolerable in terms of side effects than 5-FU containing regimens.

Keywords: Geriatric oncology, gastric cancer, capecitabine

Cite This Article: *Yılmaz Ürün Y, Mermit Erçek B. Capecitabine vs. 5-Fluorouracil: A Retrospective Study on Efficacy in Elderly Patients with Advanced Gastric Cancer. EJMI 2024;8(4):238–244.*

Gastric cancer is the third most common cause of cancer-related deaths worldwide, with more than 700,000 deaths annually.[1] A meta-analysis of three studies comparing chemotherapy with best supportive care showed a significant benefit in overall survival (OS) in favor of chemotherapy compared to supportive care alone, with median OS increasing from 4.3 months to 11 months.[2] There is no globally accepted standard chemotherapy regimen for first-line treatment of metastatic gastric cancer, and the clinical practice is variable. In a study conducted in the Netherlands, 45 different first-line systemic treatment regimens were used. Capecitabine–oxaliplatin (21%) was the most commonly administered regimen.[3] The European Society for Medical Oncology (ESMO) guidelines recommend platinum-based dual therapy as the chemotherapy regimen.[4]

5-fluorouracil (5-FU) is a nucleobase analog. It is an antineoplastic agent that acts as an antimetabolite. It enters the cells through a facilitated uracil-based transport mechanism. After conversion to active deoxynucleotides, it inhibits DNA synthesis and slows tumor growth.[5] Capecitabine

Address for correspondence: Yonca Yılmaz Ürün, MD. Department of Gastroenterology and Hepatology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Türkiye
Phone: +90 432 215 04 71 **E-mail:** dryoncayilmazurun@gmail.com

Submitted Date: November 20, 2024 **Accepted Date:** December 24, 2024 **Available Online Date:** November 16, 2025

is an oral fluoropyrimidine analog rationally designed by scientists in Japan to allow selective 5-FU activation in tumor tissues. It is a prodrug that is enzymatically converted to fluorouracil (antimetabolite) in tumors, where it inhibits DNA synthesis and slows the growth of the tumor tissue.[6] As the world population ages, the incidence of gastric cancer is increasing, and its management in the elderly population is becoming more challenging. Older patients generally have more comorbidities, shorter OS, and higher risk of complications.[7] In two trials that evaluating patients over the age of 75 and 80 with metastatic gastric cancer, the chemotherapy was effective and the side effects were well tolerated.[8, 9] Most existing guidelines on the treatment of gastric cancer are based on evidence from clinical trials in younger patients rather than in geriatric patients. However, older patients with cancer have worse OS than younger patients.[10]

The choice of chemotherapy regimen for elderly patients should be carefully evaluated, including chemotherapy efficacy and avoidance of over- or undertreatment. There is conflicting information in the literature about the efficacy and safety of 5-FU-based and capecitabine-based chemotherapy regimens for the treatment of elderly patients with metastatic gastric cancer, and they have not been adequately compared. In this study, we aimed to compare 5-FU and capecitabine regimens in terms of progression-free survival (PFS), OS, and adverse events in geriatric patients with gastric cancer.

Methods

Patients with metastatic disease at the time of diagnosis or relapsed gastric cancer treated in the oncology clinic of Van Yüzüncü Yıl University Faculty of Medicine Dursun Odabaş Medical Center between January 2006 and December 2019 were evaluated. The inclusion criteria were as follows: (1) age ≥70 years, (2) cytologically or histologically proven recurrent or metastatic gastric cancer, (3) Human Epidermal growth factor receptor 2 (HER-2)-negative tumor, (4) no prior treatment for recurrent or metastatic disease, and (5) chemotherapy regimen including capecitabine or 5-FU. The exclusion criteria were as follows: (1) age <70 years, (2) no pathological or cytological diagnosis, (3) HER-2 positive tumor, (4) any previous treatment for metastatic or recurrent disease, (5) patients receiving treatment other than chemotherapy, and (6) patients receiving chemotherapy regimens other than capitabine or 5-FU. To homogenize the patient group, HER-2 positive patients and patients receiving any treatment other than conventional chemotherapies (e.g. immunotherapies or targeted therapies) were excluded.

Patients' medical records (demographic characteristics, treatment regimens and treatment responses, grade 3-4 toxicity, progression date, date of last follow-up, and date of death) were collected. Patient performance status was assessed according to the Eastern Cooperative Oncology Group Scale (ECOG) criteria. PFS was calculated as the time from diagnosis to the date of clinical or radiologic progression. OS was calculated as the time from the date of recurrence or, if de novo metastatic, from diagnosis to death or the last follow-up.

The patients were divided into two groups: those receiving capecitabine-containing chemotherapy regimens and those receiving 5-FU-containing chemotherapy regimens. Radiologic evaluations were performed using computed tomography (CT) or Positron Emission Tomography (PET-CT) once clinical progression developed or every 8 weeks. Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Toxicity was assessed on day 1 of each cycle. Toxicity was graded according to the National Cancer Institue's the common Toxicity Criteria (NCI CTC) version 3.0.

Ethical Approval

Ethical approval was obtained from the Ethics Committee of Van Yüzüncü Yıl University Medical Faculty (decision date 08.03.2024 and No.2024/02-08). This study was conducted in accordance with the Declaration of Helsinki (revised in 2013). Informed consent was waived due to the study's retrospective design.

Statical Analysis

Statistical analyses were performed using IBM SPSS version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, ABD). Descriptive data are presented as n and % for categorical variables and mean±standard deviation for continuous variables. The distribution of variables was measured using the Kolmogorov-Smirnov test and p>0.05 was determined. Therefore, the independent t-test was used for 2-group comparisons. Pearson Chi Square test and Fisher's Exact test were used to compare categorical variables. Finally, the Kaplan-Meier method was used to compare the OS and PFS times between the chemotherapy regimen groups. A p-value <0,05 was considered statically significant level

Results

A total of 258 patients (181 men (70.2%) and 77 women (29.8%)) were enrolled in this study. The mean age was 74.4±4.2 years. Liver, lung, and peritoneal metastases were detected in 67.8 %, 18.6%, and 36% of patients, respectively. 96 patients were treated with capecitabine and 162 patients were treated with 5-FU containing regimens. The demographic characteristics, comorbidities, and metastatic status of the patients are summarized in Table 1.

Table 1. Comparison of demographical and clinical characteristics

	Total n=258 n (%)	Capacitabine n=96 n (%)	5-FU n=162 n (%)	p
Age (Mean±SD)	74.47±4.27	75.92±4.91	73.61±3.59	<0.001
Gender				
Male	181 (70.2)	58 (60.4)	123 (75.9)	0.008
Female	77 (29.8)	38 (39.6)	39 (24.1)	
Hypertension				
No	178 (69.0)	63 (65.6)	115 (71)	0.368
Yes	80 (31.0)	33 (34.4)	47 (29)	
Diabetes mellitus				
No	231 (89.5)	84 (87.5)	147 (90.7)	0.411
Yes	27 (10.5)	12 (12.5)	15 (9.3)	
ECOG				
0	38 (14.7)	11 (11.5)	27 (16.7)	0.076
1	132 (51.2)	45 (46.9)	87 (53.7)	
2	83 (32.2)	36 (37.5)	47 (29)	
3	5 (1.9)	4 (4.2)	1 (0.6)	
History of operation				
No	189 (73.3)	65 (67.7)	124 (76.5)	0.121
Yes	69 (26.7)	31 (32.3)	38 (23.5)	
Operation type				
Curative	46 (65.7)	23 (71.9)	23 (60.5)	0.319
Palliative	24 (34.3)	9 (28.1)	15 (39.5)	
Tumor localization				
Cardia	95 (37.4)	31 (33)	64 (40)	0.099
Corpus	56 (22.0)	24 (25.5)	32 (20)	
Antrum	81 (31.9)	35 (37.2)	46 (28.8)	
Diffuse	22 (8.7)	4 (4.3)	18 (11.3)	
Number of metastatic organs'				
1	153 (59.5)	62 (64.6)	91 (56.5)	0.566
2	81 (31.5)	27 (28.1)	54 (33.5)	
3	20 (7.8)	7 (7.3)	13 (8.1)	
4	3 (1.2)	0 (0)	3 (1.9)	
Liver metastasis				
No	83 (32.2)	34 (35.4)	49 (30.2)	0.390
Yes	175 (67.8)	62 (64.6)	113 (69.8)	
Lung metastasis				
No	210 (81.4)	80 (83.3)	130 (80.2)	0.538
Yes	48 (18.6)	16 (16.7)	32 (19.8)	
Bone metastasis				
No	236 (91.5)	89 (92.7)	147 (90.7)	0.584
Yes	22 (8.5)	7 (7.3)	15 (9.3)	
Peritoneal metastasis				
No	165 (64.0)	59 (61.5)	106 (65.4)	0.521
Yes	93 (36.0)	37 (38.5)	56 (34.6)	
Brain metastasis				
No	255 (99.2)	96 (100)	159 (98.8)	0.530
Yes	2 (0.8)	0 (0)	2 (1.2)	

Table 1. CONT.

	Total n=258 n (%)	Capacitabine n=96 n (%)	5-FU n=162 n (%)	p
Chemotherapy regimen				
Capecitabine	44 (17.1)	44 (45.8)	0 (0)	<0.001
FUFA	9 (3.5)	0 (0)	9 (5.6)	
FOLFOX	17 (6.6)	0 (0)	17 (10.5)	
FOLFİRİ	6 (2.3)	0 (0)	6 (3.7)	
CAPOX	14 (5.4)	14 (14.6)	0 (0)	
CX	26 (10.1)	26 (27.1)	0 (0)	
CF	16 (6.2)	0 (0)	16 (9.9)	
CP	5 (1.9)	5 (5.2)	0 (0)	
MDCF	18 (7.0)	0 (0)	18 (11.1)	
DCF	56 (21.7)	0 (0.0)	56 (34.6)	
ECF	24 (9.3)	0 (0.0)	24 (14.8)	
Others	23 (9.0)	7 (7.3)	16 (9.9)	
Progression				
No	33 (12.8)	14 (14.6)	19 (11.7)	0.507
Yes	225 (87.2)	82 (85.4)	143 (88.3)	
Mortality				
Alive	8 (3.1)	4 (4.2)	4 (2.5)	0.475
Exitus	250 (96.9)	92 (95.8)	158 (97.5)	
Average follow-up time (months) (mean±sd)	12.18±10.31	12.43±4.91	12.03±9.54	0.766

ECOG: Eastern Cooperative Oncology Group, 5-FU: 5-Fluorouracil, FUFA:5-Fluorouracil/leucoverin, FOLFOX: folinic acid -fluorouracil- oxaliplatin, FOLFIRI: folinic acid -florouracil-irinotekan, CAPOX:oxaliplatin-capecitabine, CX:cisplatin-capecitabine, CF:cisplatin-fluorouracil, CP: carboplatin-paclitaxel, mDCF:Modifiye Docetaxel-Cisplatin-Florouracil, DCF: Docetaxel-Cisplatin-Florouracil, ECF:epirubicin-cisplatin-fluorouracil.

The Median OS was 9.8 months (95% CI: 8.14-11.45) and overall median PFS was 6.2 months (95% CI: 5.21-7.18). The median OS was 9.1 months in the group receiving capecitabine and 9.9 months in the group receiving 5-FU (p=0.770). The median OS did not differ significantly between the chemotherapy groups. Similarly, the median PFS (months) according to the chemotherapy regimen group was not statistically significant (p=0.696). OS and PFS rates of the patients are summarized in Table 2.

The most common treatment-related adverse events were neutropenia (22.1%), anemia (18.9%), and nausea and vomiting (14%). Other adverse event rates are shown in table 3. Grade 3-4 neutropenia (p<0.001), Grade 3-4 ane-

Table 2. Comparison of overall survival and progression-free survival results of patients

Overall survival (months)	2-year survival %	5-year survival %	Median (%95 CI)	P
Overall	11.2	5.0	9.80 (8.14-11.45)	
Chemotherapy Regimen				
Capecitabine	12.9	1.5	9.10 (6.52-11.67)	0.770
5-Fluorouracil	10.2	0.0	9.93 (7.56-12.29)	
Progression free survival (months)	**2-year survival %**	**5-year survival %**	**Median (%95 CI)**	**p**
All patients	4.4	0.9	6.20 (5.21-7.18)	
Chemotherapy Regimen				
Capecitabine	2.1	2.1	6.20 (4.17-8.22)	0.696
5-Fluorouracil	5.5	-	6.20 (5.04-7.35)	

Table 3. Comparison of side effects between groups

	Total (n=258) n (%)	Capecitabine (n=96) n (%)	5-Fluorouracil (n=162) n (%)	p
Grade 3-4 Neutropenia				
No	198 (77.6)	85 (89.5)	113 (70.6)	<0.001
Yes	57 (22.1)	10 (10.5)	47 (29.4)	
Grade 3-4 Anemia				
No	206 (81.1)	83 (87.4)	123 (77.4)	0.049
Yes	48 (18.9)	12 (12.6)	36 (22.6)	
Grade 3-4 Trombositopenia				
No	240 (94.9)	93 (98.9)	147 (92.5)	0.035
Yes	13 (5.1)	1 (1.1)	12 (7.5)	
Febrile Neutropenia				
No	234 (92.1)	92 (96.8)	142 (89.3)	0.031
Yes	20 (7.9)	3 (3.2)	17 (10.7)	
Grade 3-4 hand-foot syndrome				
No	237 (92.9)	89 (93.7)	148 (92.5)	0.721
Yes	18 (7.1)	6 (6.3)	12 (7.5)	
Grade 3-4 diarrhea				
No	236 (92.5)	86 (90.5)	150 (93.8)	0.343
Yes	19 (7.5)	9 (9.5)	10 (6.3)	
Grade 3-4 Paresthesia				
No	242 (95.3)	89 (93.7)	153 (96.2)	0.373
Yes	12 (4.7)	6 (6.3)	6 (3.8)	
Grade 3-4 nausea and vomiting				
No	221 (86.0)	83 (86.5)	138 (85.7)	0.868
Yes	36 (14.0)	13 (13.5)	23 (14.3)	
Hypersensitivity				
No	252 (98.8)	95 (100)	157 (98.1)	0.296
Yes	3 (1.2)	0 (0)	3 (1.9)	
Thrombosis				
No	239 (93.4)	91 (94.8)	148 (92.5)	0.476
Yes	17 (6.6)	5 (5.2)	12 (7.5)	
Renal toxicity				
No	243 (95.3)	90 (94.7)	153 (95.6)	0.766
Yes	12 (4.7)	5 (5.3)	7 (4.4)	
Hepatic toxicity				
No	251 (99.6)	92 (98.9)	159 (100)	0.369
Yes	1 (0.4)	1 (1.1)	0 (0)	
Cardiotoxicity				
No	252 (98.0)	96 (100)	155 (96.9)	0.160
Yes	5 (2.0)	0 (0)	5 (3.1)	

mia (p=0.049), Grade 3-4 thrombocytopenia (p=0.035), and febrile neutropenia (p=0.031) were more frequent in the 5-FU group.

Discussion

In our study, we found no statistically significant difference in PFS and OS between 5-FU-containing regimens and capecitabine-containing regimens in the first-line treatment of patients aged ≥70 years with relapsed or metastatic gastric cancer at diagnosis. However, grade 3-4 neutropenia, anemia, thrombocytopenia, and febrile neutropenia were significantly higher in the 5-FU group.

In a meta-analysis of REAL-2 and ML17032 studies, OS was superior in patients with advanced esophagogastric can-

cer treated with capecitabine combinations than in those treated with 5-FU combinations.[11] In a study that included 85 patients comparing the epirubicin, cisplatin, and 5-FU infusion (ECF) regimen with the epirubicin, cisplatin, and capecitabine (ECX) regimen in patients with advanced or metastatic gastric cancer, the ECX regimen was shown to be at least as effective as the ECF regimen, with a similar tolerability profile.[12] In a randomized phase 3 study comparing cisplatin+oral capecitabine (XP) or 5-FU continuous infusion (FP) as first-line treatment for advanced gastric cancer, the XP regimen was found to be significantly non-inferior to FP for PFS.[13] In a study evaluating 1002 patients with untreated advanced esophagogastric cancer, the patients were divided into four groups. The first, second, third, and fourth groups were randomly assigned to ECF, ECX, epirubicin-oxaliplatin-fluorouracil (EOF), and epirubicin-oxaliplatin-capecitabine (EOX) regimens, respectively. Compared with 5-FU, triple therapy with capecitabine was not superior in OS (median OS times of 9.9 months, 9.9 months, 9.3 months and 11.2 months, respectively). PFS and treatment response rates did not differ significantly between the regimens. The toxic effects of capecitabine and 5-FU were similar.[14] In our study, the median OS was 9.8 months and the median PFS was 6.2. Median OS was 9.1 months in the capecitabine group and 9.9 months in the 5-FU group. The median PFS was 6.2 months in both groups, which is consistent with the available literature.[15-17]

In a study evaluating the efficacy and toxicity of oral capecitabine and 5-FU as first-line therapy in patients with metastatic colorectal cancer, significantly lower rates of neutropenia, diarrhea, stomatitis, nausea and alopecia were observed in patients receiving capecitabine. Hand-foot syndrome and hyperbilirubinemia were observed more frequently in patients receiving capecitabine.[18] A meta-analysis investigating the effect of capecitabine versus 5-FU in patients with advanced gastric cancer included eight randomized controlled trials involving a total of 1998 patients with advanced gastric cancer, 982 with capecitabine, and 1016 with 5-FU. Compared to 5-FU, capecitabine treatment was significantly associated with a reduced risk of neutropenia and stomatitis in patients with advanced gastric cancer. In terms of side effects, capecitabine was associated with a higher rate of hand-foot syndrome than 5-FU. The rates of thrombocytopenia, nausea and vomiting, alopecia, and diarrhea were similar between the capecitabine and 5-FU groups.[19] In our study, the incidence of grade 3-4 neutropenia, grade 3-4 anemia, grade 3-4 thrombocytopenia, and febrile neutropenia was higher in the 5-FU group. There were no differences in terms of other side effects.

Based on these findings, it can be concluded that regimens using capecitabine instead of 5-FU have at least as good efficacy as 5-FU, have fewer side effects, and require fewer hospital admissions due to the fact that capecitabine is administered orally and does not require an infusion pump, thereby improving treatment adherence and quality of life.

Study Limitations

Although our study has limitations, such as being single-center and retrospective, the long-term follow-up of the patients and the fact that the study was conducted in a geriatric patient group makes our study valuable.

Conclusion

In conclusion, using real-life data, we found that capacitabine is as effective as 5-FU and has fewer grade 3-4 side effects in geriatric patients with advanced gastric cancer. Large-scale and multicenter prospective studies with larger numbers of patients are needed to evaluate the efficacy and tolerability of capacitabine and 5-FU in geriatric patients with metastatic gastric cancer.

Disclosures

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Van Yüzüncü Yıl University Medical Faculty (decision date 08.03.2024 and No.2024/02-08).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept (YYÜ, BME), Design (YYÜ, BME), Data Collection and/or processing (BME), Analysis and/or interpretation (BME, YYÜ). All the authors approved the final version of the manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians 2021;71(3):209-249.
2. Wagner AD, Syn NL, Moehler M, Grothe W, Yong WP, Tai BC,, et al. Chemotherapy for advanced gastric cancer. Cochrane database of systematic reviews, 2017(8).
3. Dijksterhuis WPM, Verhoeven RHA, Slingerland M, Haj Mohammad N, de Vos-Geelen J, Beerepoot LV, et al. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: a real-world evidence study. International journal of cancer 2020;146(7):1889-1901.
4. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology 2022;33(10):1005-1020.
5. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nature reviews cancer

2003;3(5):330-338.
6. Walko CM, Lindley C. Capecitabine: a review. Clin Ther 2005;27(1):23-44.
7. Sedrak MS, Freedman RA, Cohen HJ, Muss HB, Jatoi A, Klepin HD, et al., Older adult participation in cancer clinical trials: a systematic review of barriers and interventions. CA: a cancer journal for clinicians 2021;71(1):78-92.
8. Sezgin Y, Urun Y. Chemotherapy Efficacy and Tolerability in Metastatic Gastric Cancer Patients Aged 75 Years and Older. EJMI 2023;7(4):487-493
9. Güner G, Ürün M. Comparison of efficacy and tolerability of single agent and double agent chemotherapy regimens in first-line treatment of elderly patients with HER-2 negative metastatic gastric cancer. J Curr Hematol Oncol Res 2024;2(1):15-19.
10. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. The Lancet 2011;377(9760):127-138.
11. Okines AFC, Norman AR, McCloud P, Kang YK, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Annals of oncology 2009;20(9):1529-1534.
12. Ocvirk J, Reberšek M, Skof E, Hlebanja Z, Boc M. Randomized prospective phase II study to compare the combination chemotherapy regimen epirubicin, cisplatin, and 5-fluorouracil with epirubicin, cisplatin, and capecitabine in patients with advanced or metastatic gastric cancer. American Journal of Clinical Oncology;2012;35(3):237-241.
13. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Annals of oncology 2009;20(4):666-673.
14. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. New England Journal of Medicine 2008;358(1):36-46.
15. Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. Journal of clinical oncology;2008;26(9):1435-1442.
16. Liu ZF, Guo QS, Zhang XQ, Yang XG, Guan F, Fu Z, et al. Biweekly oxaliplatin in combination with continuous infusional 5-fluorouracil and leucovorin (modified FOLFOX-4 regimen) as first-line chemotherapy for elderly patients with advanced gastric cancer. American journal of clinical oncology 2008;31(3):259-263.
17. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. The lancet oncology 2008;9(3):215-221.
18. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. Journal of Clinical Oncology 2001;19(8):2282-2292.
19. Wu Z, Zhang X, Zhang C, Lin Y. Meta-Analysis of Capecitabine versus 5-Fluorouracil in Advanced Gastric Cancer. Evidence-Based Complementary and Alternative Medicine 2023;(1):4946642.