Article published online: 2024-09-30

Original Article

Efficacy and Safety of First-Line Palliative Chemotherapy with Fluorouracil Plus Leucovorin, Oxaliplatin, and Docetaxel (FLOT) in HER2-Negative Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma: A Single-Institutional Real-World Experience from Eastern India

Tamojit Chaudhuri[1] Jaishree Bankira[1] Amitabh Kumar Upadhyay[1] Rahul Panda[1] Vanita Pandey[2] Sujata Mitra[3] Sopia Mukherjee[4]

[1] Department of Medical Oncology, Meherbai Tata Memorial Hospital, Jamshedpur, Jharkhand, India
[2] Department of Pathology, Meherbai Tata Memorial Hospital, Jamshedpur, Jharkhand, India
[3] Department of Nuclear Medicine, Meherbai Tata Memorial Hospital, Jamshedpur, Jharkhand, India
[4] Department of Microbiology, Manipal Tata Medical College, Jamshedpur, Jharkhand, India

Address for correspondence Tamojit Chaudhuri, MBBS, MD, DM, Department of Medical Oncology, Meherbai Tata Memorial Hospital, OPD Room 5, Jamshedpur, Jharkhand, India, Pin 831001 (e-mail: tamojit.cnmc@gmail.com).

South Asian J Cancer

Abstract


Tamojit Chaudhuri

Background Fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) is one of the preferred perioperative chemotherapy regimens in locally advanced resectable gastric cancer (GC). Till date, there are very few published data from India, regarding the outcomes of this relatively well-tolerated biweekly triplet regimen as first-line palliative chemotherapy in metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Materials and Methods In the present retrospective study, we evaluated the efficacy and safety of first-line FLOT regimen in Indian patients with HER2-negative metastatic adenocarcinoma of stomach or GEJ. The primary endpoint was overall survival (OS). Progression-free survival (PFS), overall response rate (ORR), and toxicity profile were taken as secondary endpoints.

Results Between January 2021 and June 2024, 88 patients were treated with FLOT. The median age was 52 years (range, 23–68); 69.3% were males and 37.5% of the patients had ≥ 3 metastatic disease sites involvement at baseline. Dose reductions due to toxicity were required in 25% of the patients. The ORR was 68.2%; median PFS and OS were 6.3 months (95% confidence interval [CI]: 5.3–7.4) and 12.5 months (95% CI: 11.3–14.2), respectively. The most frequent grade 3 to 4 adverse events were diarrhea (15.9%), fatigue (13.6%), and neutropenia (12.5%). Younger patients (aged < 55 years)

Keywords
- gastric cancer
- systemic chemotherapy
- FLOT regimen

DOI https://doi.org/10.1055/s-0044-1791524 ISSN 2278-330X

How to cite this article: Chaudhuri T, Bankira J, Upadhyay AK, et al. Efficacy and Safety of First-Line Palliative Chemotherapy with Fluorouracil Plus Leucovorin, Oxaliplatin, and Docetaxel (FLOT) in HER2-Negative Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma: A Single-Institutional Real-World Experience from Eastern India. South Asian J Cancer 2024;00(00):00–00.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

had much less ≥ grade 3 diarrhea (7.5%, $n = 4$), compared with patients aged ≥ 55 years (28.6%, $n = 10$). There was one toxicity-related death.

Conclusion In the present study, biweekly FLOT regimen with primary prophylactic granulocyte colony-stimulating factor demonstrated encouraging efficacy with a favorable nongastrointestinal toxicity profile in Indian patients with HER2-negative metastatic gastric or GEJ adenocarcinoma. Clearly, this well-tolerated triplet regimen should be explored further through large prospective randomized trials in Asian patients.

Introduction

Gastric cancer (GC) is the fifth most common type of cancer worldwide, and remains the fourth leading cause of cancer-related mortality.[1] It is a major health care challenge in many Asian countries and is often diagnosed at advanced and/or metastatic stage.[2] Metastatic GC has a poor prognosis with a median survival of only 3 to 5 months, with best supportive care (BSC).[3,4] In several randomized trials, systemic chemotherapy has shown improved survival and quality of life parameters compared with BSC alone in patients with advanced inoperable and/or metastatic GC.[3–5] Many conventional chemotherapy agents are effective as first-line palliative systemic therapy in these patients, like fluoropyrimidines, platinums, epirubicin, taxanes, and irinotecan.[3–8] But, due to unsatisfactory results, no optimal first-line palliative systemic therapy regimen has emerged. As per currently available European or pan-Asian guidelines, doublet platinum/fluoropyrimidine (PF) combinations or triplet regimens comprising of PF plus taxane, are recommended as first-line chemotherapy in fit patients with HER2-negative advanced inoperable or metastatic GC.[9,10]

The incremental gain in survival outcomes, which could be achieved by addition of a third chemotherapy drug (e.g., epirubicin or docetaxel) with PF doublet, has been investigated in various trials.[8,11–15] In a meta-analysis, Wagner et al showed a significant survival benefit with addition of anthracycline to PF doublet in Western population.[14] But later on, in a randomized phase II study including Asian patients, the addition of epirubicin to a PF combination failed to improve response rate or survival.[15] In phase III V325 trial, the triplet combination of docetaxel, cisplatin, and 5-fluorouracil (5-FU) (DCF) improved survival of advanced GC patients compared with cisplatin/5-FU, but at the cost of increased toxicity especially involving febrile neutropenia.[12] Few recent Asian trials have shown the effectivity and improved toxicity profile of a modified triplet regimen consisting of docetaxel plus PF.[16–18] However, substantial toxicity remains a major concern which prevents the routine use of first-line docetaxel plus PF triplet combination regimens in metastatic GC.

After the publication of a pivotal phase II/III study in 2019, the fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) regimen has become the standard choice for perioperative chemotherapy in locally advanced, resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma; solely because of the improved survival and acceptable toxicity profile of FLOT regimen in this setting.[19–21] There is a real scarcity of published data regarding the outcomes of first-line FLOT regimen in metastatic GC, particularly from India.[22,23] To the best of our knowledge, this is the largest reported data set of FLOT regimen in Indian patients with metastatic gastric or GEJ adenocarcinoma.

Materials and Methods

Patient selection: This single-institutional retrospective analysis of prospectively collected data, was planned to evaluate the efficacy and safety of first-line palliative chemotherapy with FLOT regimen in Indian patients with HER2-negative metastatic adenocarcinoma of stomach or GEJ. Patients older than 18 years of age were eligible for inclusion in this study if they had, histologically confirmed metastatic adenocarcinoma of the stomach or GEJ; Eastern Cooperative Oncology Group performance status ≤ 1; adequate renal, hepatic, and hematologic function; and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Major exclusion criteria were: Siewert type 1 GEJ cancers, previous chemotherapy for metastatic or locally advanced disease, poor organ function, concurrent second malignancy, evidence of brain metastases, and HER2-positive tumors.

Treatment assignment: The patients received standard FLOT regimen;[20] consisted of 50 mg/m^2 docetaxel (1-hour intravenous infusion) on day 1, 85 mg/m^2 oxaliplatin (2-hour intravenous infusion) on day 1, 200 mg/m^2 leucovorin (2-hour intravenous infusion) on day 1, followed by 5-FU 2600 mg/m^2 (24-hour continuous intravenous infusion) on day 1, administered every 2 weekly. All the patients also received appropriate premedication and primary prophylactic granulocyte colony-stimulating factor (G-CSF). A 20% dose reduction in subsequent cycles was done in patients developing any ≥ grade 3 toxicity. First-line chemotherapy was continued until disease progression, unacceptable toxicity, or patient withdrawal. A planned discontinuation of oxaliplatin was followed after 10th cycle of first-line FLOT regimen in patients who were still responding, to prevent cumulative neurotoxicity of oxaliplatin.

Evaluation and outcomes: Before treatment initiation, a complete evaluation was performed; including full medical

history, physical examination, complete blood count, serum biochemical analysis, electrocardiography, two-dimensional echocardiography, upper gastrointestinal (GI) endoscopy, and contrast-enhanced computed tomography (CECT) of the thorax, abdomen, and pelvis or whole-body positron-emission tomography-CT (PET-CT). CECT/PET-CT scans were repeated after 4 and 8 cycles of first-line palliative chemotherapy, as a routine response evaluation strategy. Subsequent radiologic evaluations have been performed every 12 weeks (±2 weeks) or whenever needed depending on the symptoms. Responses to chemotherapy were reported according to the RECIST version 1.1. Treatment-related toxicities were classified based on the Common Terminology Criteria for Adverse Events version 4.0. The primary endpoint was overall survival (OS). Progression-free survival (PFS), overall response rate (ORR), and toxicity profile were taken as secondary endpoints.

Statistical analysis: Categorical variables were depicted as counts and percentages; continuous variables were depicted as medians and range. The Kaplan–Meier method was used to evaluate the PFS and OS estimates. All statistical analyses have been done using IBM SPSS version 17.0.

Ethics: All clinical procedures were performed in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2013. A formal approval from the Institutional Ethics Committee was not required for retrospective studies, as per our Institutional protocol. Informed consent was obtained from each patient before initiation of palliative chemotherapy.

Results

Patient characteristics: Between January 2021 and June 2024, 88 patients were included in this study at the department of medical oncology of our hospital. The baseline demographic characteristics are presented in ►Table 1. Molecular profiling was done in 22 patients (25%), none of them showed mismatch repair deficient/microsatellite instability (MSI)-high status. Six patients (27.3%) had programmed death-ligand 1 (PDL-1) combined positive score (CPS) > 1, and none of them received immunotherapy-based regimen due to affordability issues.

Chemotherapy characteristics: A total 729 cycles of first-line FLOT regimen were administered, with a median of 8 chemotherapy cycles per patient (range, 1–24). Treatment delays happened in 208 (28.5%) FLOT cycles, with a median of 4 days delay per cycle (range, 1–12). Dose reductions of docetaxel and 5FU due to toxicity were done in 22 patients (25%). Postprogression, 54 patients (61.4%) received second-line palliative chemotherapy with either irinotecan monotherapy ($n = 47$) or FOLFIRI regimen ($n = 7$).

Efficacy and survival: The ORR after 4 cycles of FLOT regimen was 68.2% (2.2% complete response [CR] and 66% partial response [PR]). Disease stabilization was achieved in 22.7% of patients. At a median follow-up of 17 months for the entire cohort, the median PFS was 6.3 months (95% confidence interval [CI]: 5.3–7.4) (►Fig. 1), while the median OS was 12.5 months (95% CI: 11.3–14.2) (►Fig. 2). Multivariate analysis demonstrated that demographic parameters including gender, site of primary tumor, site, and number of metastatic sites had no significant impact on survival outcomes.

Table 1 Patient characteristics at baseline

Variables	FLOT regimen ($n = 88$)
Median age in years (range)	52 (23–68)
< 55	53 (60%)
≥ 55	35 (40%)
Male gender	61 (69.3%)
Site of primary tumor	
GEJ Siewert type 2 or 3	16 (18%)
Body of the stomach	51 (58.1%)
Pylorus and antrum	21 (23.9%)
WHO grade of primary tumor	
Grade I	4 (4.5%)
Grade II	32 (36.4%)
Grade III	52 (59.1%)
Site of metastases	
Liver	37 (42%)
Nonregional lymph node	34 (38.6%)
Omento-peritoneal deposits ± ascites	32 (36.4%)
Lungs	10 (11.4%)
Ovary	8 (9%)
Bone	3 (3.4%)
Number of metastatic sites involved	
1	14 (16%)
2	41 (46.5%)
≥ 3	33 (37.5%)
Baseline requirement of nasojejunal tube or feeding jejunostomy tube placement	21 (23.9%)

Abbreviations: FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; WHO, World Health Organization.

Toxicity profile: The majority of hematological and non-hematological adverse events were of grade 1 and 2 (►Table 2). The most frequent grade 3 to 4 adverse events were diarrhea (15.9%), fatigue (13.6%), neutropenia (12.5%), and anemia (10.2%). One patient died of treatment-related toxicity after the first cycle of FLOT.

Discussion

This retrospective study aimed to evaluate the efficacy and safety of first-line palliative chemotherapy with biweekly FLOT regimen in Indian patients with HER2-negative metastatic gastric or GEJ adenocarcinoma. In light of the data from existing medical literature, it is widely accepted that the

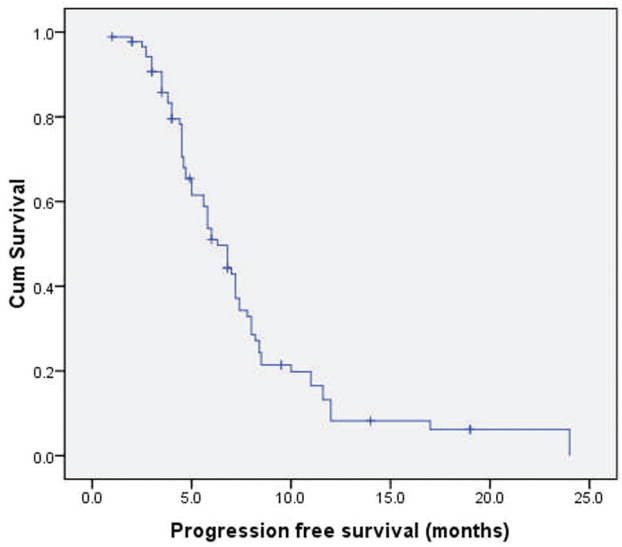

Fig. 1 Kaplan–Meier estimates of progression-free survival (in months) of the patients ($n = 88$) treated with fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) regimen.

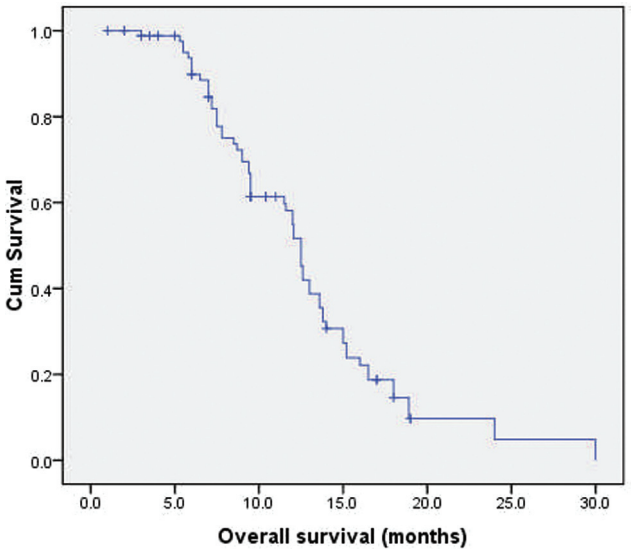

Fig. 2 Kaplan–Meier estimates of overall survival (in months) of the patients ($n = 88$) treated with fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) regimen.

triplet combination of docetaxel plus PF is probably the most efficacious regimen in fit patients with metastatic GC, but at the cost of substantial grade 3 or 4 toxicity.[12,13,16–18] As per the currently available medical literature, there are very few published Indian and Western data regarding the efficacy and safety of FLOT regimen in metastatic GC.[22–25]

In a prospective study from South India by Srinivasalu et al, 28 patients of metastatic ($n = 25$) and locally advanced ($n = 3$) gastric adenocarcinoma received FLOT chemotherapy.[22] The mean number of chemotherapy cycles per patient was 4.5, and 75% of patients received at least 4 cycles of FLOT. The ORR was 52.7%, with PR being the best-achieved response. The median PFS was 5 months and median OS was

Table 2 Toxicity profile

Variables	FLOT regimen ($n = 88$)	
	All grades	Grade 3–4
Anemia	63 (71.6%)	9 (10.2%)
Neutropenia	23 (26.1%)	11 (12.5%)
Febrile neutropenia	5 (5.7%)	5 (5.7%)
Thrombocytopenia	24 (27.2%)	–
Nausea	31 (35.2%)	–
Vomiting	21 (23.8%)	–
Stomatitis or mucositis	28 (31.8%)	–
Diarrhea	49 (55.7%)	14 (15.9%)
Constipation	7 (7.9%)	–
Serum AST	19 (21.6%)	–
Serum ALT	20 (22.7%)	–
Peripheral sensory neuropathy	25 (28.4%)	–
Myalgia or arthralgia	40 (45.4%)	9 (10.2%)
Fatigue	63 (71.6%)	12 (13.6%)
Alopecia	35 (39.8%)	–
Toxicity-related death	1 (1.1%)	1 (1.1%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel.

13 months.[22] The most common toxicities were, all-grade neutropenia (75%), febrile neutropenia (35.7%), fatigue (35.7%), and mucositis (35.7%). Sixteen (57.1%) patients needed dose modifications due to treatment-related toxicity.[22] In another single-institute prospective study by the same authors, 25 patients with metastatic adenocarcinoma of stomach received modified FLOT regimen.[23] The reported ORR was 52% (CR in 1 patient and PR in 12 patients), and 1-year PFS was 60%. Febrile neutropenia, mucositis, and thrombocytopenia were the predominant toxicities, and dose modifications were done in 60% of patients.[23] Both of these abovementioned Indian studies[22,23] used a modified dose of 5-FU, which was 1,200 mg/m^2/day as a 24-hour infusion on days 1 and 2 (as opposed to 2,600 mg/m^2 on day 1 over 24 hours in the landmark phase II study by Al-Batran et al[24]). Prophylactic myeloid growth factor administration was permitted, but not mandatory.[22,23]

The FLOT regimen was originally developed in Europe, to incorporate docetaxel into a relatively better tolerable biweekly oxaliplatin-based chemotherapy regimen, in patients with metastatic adenocarcinoma of stomach or GEJ.[24] In the landmark phase II study by Al-Batran et al including 54 patients of metastatic gastric or GEJ adenocarcinoma, FLOT regimen achieved an ORR of 57.7%, median PFS of 5.2 months, and median OS of 11.1 months.[24] High $\geq$ grade 3 toxicity rates were reported in this trial, especially involving neutropenia (48.1%), leukopenia (27.8%), diarrhea (14.8%), and fatigue (11.1%). But, complicated neutropenia rate was only 3.8%; and none of the patients in this study received

primary prophylactic myeloid growth factors.[24] In a randomized study, Al-Batran et al evaluated the feasibility and tolerability of FLOT versus FLO regimen (infusional 5-FU, leucovorin, and oxaliplatin) in 143 elderly patients (aged >65 years) with advanced/metastatic esophagogastric cancers.[25] FLOT was associated with more grade ¾ toxicity than FLO (FLOT, 81.9%; FLO, 38.6%; $p<0.001$), particularly involving alopecia, neutropenia, leukopenia, diarrhea, and nausea.[25] The ORR and PFS were better in the FLOT arm in the subgroup of patients aged between 65 and 70 years but not in patients aged 70 years and older. Finally, the authors concluded that, triplet chemotherapy with FLOT regimen was feasible in elderly patients with advanced esophagogastric cancer, but at the cost of significantly increased toxicity in patients aged $\geq$ 70 years.[25] The reported rates of $\geq$ grade 3 neutropenia and infection were very high (52.8 and 18.1%, respectively) with FLOT regimen in this study, which were explainable to some extent due to the selective accrual of elderly patients (median age 69 years) and avoidance of primary prophylactic G-CSF.[25]

As a component of palliative chemotherapy regimens in patients with metastatic GC, oxaliplatin has similar efficacy but favorable toxicity profile, compared with cisplatin.[26,27] Among the two available fluoropyrimidine drugs in India, capecitabine is noninferior to infusional 5-FU in terms of efficacy.[28] However, infusional 5-FU is also routinely used in India and other Asian countries, particularly in patients who cannot manage frequent intake of oral pills due to feeding via nasojejunal (NJ)/feeding jejunostomy (FJ) tube. In the present study, 21 patients (23.9%) required NJ or FJ tube placement at baseline due to gastric inlet or outlet obstruction.

Few unique demographic characteristics of the patient population of the current study need to be highlighted, for example, inclusion of a patient cohort of at least a decade younger than included in most published global studies, a low proportion of proximal GC primaries, and a significantly high percentage of high-volume metastatic disease at baseline. In our study, the reported ORR and survival outcomes of FLOT regimen in metastatic GC were almost comparable to those of the previously published data.[22–25] The $\geq$ grade 3 neutropenia and febrile neutropenia rates (12.5 and 5.7%, respectively) were low in our study, probably due to the mandatory administration of primary prophylactic pegylated G-CSF. The $\geq$ grade 3 diarrhea rate was unacceptably high in the present study (15.9%, $n=14$), and was the most common treatment-related toxicity resulted in dose reductions of docetaxel and 5FU. Similarly, increased GI toxicities were also reported in other Indian studies, with FLOT regimen.[22,23] The probable reason for this is multifactorial, as a significant proportion of our patients belong to lower socioeconomic classes and had a significant weight loss at baseline. Further analysis suggested that $\geq$ grade 3 diarrhea predominantly happened in patients aged $\geq$ 55 years (28.6%, $n=10$), in comparison to younger patients (7.5%, $n=4$). The overall toxicity profile of FLOT regimen in our study was favorable, compared with other docetaxel-based triplet combinations in East Asian patients (e.g., DOF, DCF, or DOX).[17,18,29]

In our study, multivariate analysis suggested that none of the covariates had any significant impact on survival outcomes. The probable reasons are multiple—for example, exploratory nature of the covariates, retrospective nature of this study, and excellent efficacy of FLOT regimen in all the subgroups. Molecular profiling was done in only 25% of the patients, which revealed a low incidence of MSI-high status and PDL-1 CPS >1 in 27.3% of patients; comparable with the reported data from other Indian centers.[29,30] The fact that none of the patients ($n=6$) with PDL-1 CPS >1 status received immunotherapy, again highlights the real-world nature of this data from resource-constrained setting of Eastern India. Certain limitations of our study must be highlighted, for example, retrospective single-center design, low sample size, and a lower-than-expected percentage of patients receiving subsequent lines of palliative chemotherapy.

Conclusion

In the current study, biweekly FLOT regimen with primary prophylactic G-CSF, demonstrated significant clinical activity with a favorable non-GI toxicity profile in Indian patients with metastatic gastric and GEJ adenocarcinoma. The response rates and survival outcomes of this regimen were quite comparable with those of the commonly used triplet regimens comprising of docetaxel plus PF. The major safety concern was increased GI toxicity, particularly in elderly patients with not-so-good performance score. In our opinion, FLOT can be considered as one of the preferred first-line palliative regimens, in properly selected patients with Her2-neu negative advanced/metastatic gastric or GEJ adenocarcinoma. Clearly, these encouraging findings of this relatively tolerable biweekly protocol should be tested and validated further, through large prospective randomized trials in Asian patients.

Authors' Contributions

T.C., J.B., A.K.U., R.P., V.P., and S.M. were involved in data collection, conception and design of the manuscript, manuscript writing, statistical analysis, and drafting. Additionally, S.M. specifically contributed to manuscript writing, statistical analysis, and drafting.

Conflict of Interest

None declared.

References

1 Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(03): 209–249
2 Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends–an update. Cancer Epidemiol Biomarkers Prev 2016;25(01):16–27
3 Glimelius B, Ekström K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997;8 (02):163–168
4 Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in

patients with non-resectable gastric cancer. Br J Cancer 1995;71 (03):587–591
5 Bouché O, Raoul JL, Bonnetain F, et al; Fédération Francophone de Cancérologie Digestive Group. 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(21):4319–4328
6 Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010;17 (03):CD004064
7 The Gastrointestinal Tumor Study Group. Randomized study of combination chemotherapy in unresectable gastric cancer. Cancer 1984;53(01):13–17
8 Bamias A, Hill ME, Cunningham D, et al. Epirubicin, cisplatin, and protracted venous infusion of 5-fluorouracil for esophagogastric adenocarcinoma: response, toxicity, quality of life, and survival. Cancer 1996;77(10):1978–1985
9 Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold DESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27(Suppl 5):v38–v49
10 Muro K, Van Cutsem E, Narita Y, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann Oncol 2019;30(01): 19–33
11 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(01):261–267
12 Van Cutsem E, Moiseyenko VM, Tjulandin S, et al; V325 Study Group. 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(31):4991–4997
13 Roth AD, Fazio N, Stupp R, et al; Swiss Group for Clinical Cancer Research. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007;25(22):3217–3223
14 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 (18):2903–2909
15 Yun J, Lee J, Park SH, et al. A randomised phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in advanced gastric cancer. Eur J Cancer 2010;46(05):885–891
16 Liang R, Chen X-Y, Lin Y, et al. Clinical efficacy and safety of standard versus modified DCF regimens in treatment of advanced gastric cancer. Int J Exp Med 2016;9:9404–9410
17 Liu M, Hu G, Wang Y, et al. Comparison of FOLFOX and DOF regimens as first-line treatment in East Asian patients with advanced gastric cancer. OncoTargets Ther 2018;11:375–381
18 Babu KG, Chaudhuri T, Lakshmaiah KC, et al. Efficacy and safety of first-line systemic chemotherapy with epirubicin, cisplatin plus 5-fluorouracil and docetaxel, cisplatin plus 5-fluorouracil regimens in locally advanced inoperable or metastatic gastric or gastroesophageal junction adenocarcinoma: a prospective phase II study from South India. Indian J Cancer 2017;54(01):47–51
19 Al-Batran SE, Homann N, Pauligk C, et al; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019;393(10184):1948–1957
20 NCCN guidelines Version 2. 2022 Gastric Cancer. Accessed September 30, 2022 at: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
21 Bhargava P, Das S, Ostwal V, et al. An analysis of tolerance and early survival outcomes with perioperative modified FLOT in gastric cancers. South Asian J Cancer 2022;11(02):112–117
22 Srinivasalu VK, Philip A, Pillai R, Jose WM, Pavithran K. A prospective study to evaluate the efficacy of the fluorouracil, leucovorin, oxaliplatin and docetaxel chemotherapy regimen in patients with locally advanced and metastatic adenocarcinoma of stomach. Indian J Med Paediatr Oncol 2022;43:153–158
23 Srinivasalu VK, Subramaniam N, Jose WM, Philip A, Pavithran K. mFLOT versus EOX in first line treatment of metastatic carcinoma of stomach. Ann Oncol 2018;29(09):ix52
24 Al-Batran SE, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008;19(11):1882–1887
25 Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). Eur J Cancer 2013;49(04):835–842
26 Ryu M-H, Park YI, Chung I-J, et al. Phase III trial of s-1 plus oxaliplatin (SOX) vs s-1 plus cisplatin (SP) combination chemotherapy for first-line treatment of advanced gastric cancer (AGC): SOPP study. J Clin Oncol 2016;34:4015
27 Yamada Y, Higuchi K, Nishikawa K, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. Ann Oncol 2015;26(01): 141–148
28 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. Ann Oncol 2009;20(09):1529–1534
29 Ramaswamy A, Bhargava P, Dubashi B, et al. Docetaxel-oxaliplatin-capecitabine/5-fluorouracil (DOX/F) followed by docetaxel versus oxaliplatin-capecitabine/5-fluorouracil (CAPOX/FOLFOX) in HER2-negative advanced gastric cancers. JNCI Cancer Spectr 2024;8(04):pkae054
30 Anand R, Rauthan A, Patil P, Murthy NY. Molecular testing in stage 4 stomach cancer in India: a single-centre experience. Cureus 2023;15(11):e49412

