Article published online: 2024-07-22

Original Article

Efficacy and Safety of mFOLFOX-6 in Advanced Gastric Cancer: A Prospective Observational Study

Amrith B. Patel[1] Varun Goel[1] Srujana Joga[1] V.P.B. Koyyala[1,2] Sumit Goyal[1] Dinesh C. Doval[1] Ullas Batra[1] Vineet Talwar[1]

[1] Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India
[2] Department of Medical Oncology, Assam Cancer Trust Hospital, Tejpur, Assam, India

Address for correspondence Amrith B. Patel, MD, DrNB, Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi 110085, India (e-mail: amrithpatel@gmail.com).

South Asian J Cancer

Abstract

Amrith B. Patel

Background The widespread use of oxaliplatin plus infusional 5-fluorouracil (5-FU) and folinic acid (FOLFOX) in advanced gastric cancers is mainly based on clinical trials conducted at Western/European countries. The prospective data on efficacy and safety of FOLFOX in advanced gastric cancer is lacking from the developing countries. In this prospective observational study, we evaluated the efficacy and toxicity of mFOLFOX-6 in patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinomas, as first-line palliative chemotherapy.

Methods Patients with previously untreated metastatic adenocarcinoma of stomach/GEJ, received mFOLFOX-6 (2 hours infusion of oxaliplatin [85 mg/m^2] and folinic acid [400 mg/m^2], followed by fluorouracil 400 mg/m^2 intravenous push, then a 46-hour continuous infusion of 5-FU [2,400 mg/m^2]). Cycles were repeated every 2 weeks. The patients were prospectively followed up for response rates and toxicity.

Results Sixty-six patients were included in the study with a median age of 57 years. Sixty-two patients were evaluable for response. The overall response rate was 53%, with a disease control rate (overall response and stable disease) of 81.8%. The median progression-free survival was 6 months (95% confidence interval [CI] 5.2–6.7 months) and the median overall survival was 11.5 months (95% CI 9.0–13.9 months). Ascites at presentation and more than one site of metastasis are associated with significantly lower survival on the log-rank test. Gastrointestinal and hematological toxicities were predominant, with rates of grade 3 to 4 nausea/vomiting (13.6%), anemia (15.1%), and neutropenia (13.6%). Among other toxicities, neurosensory toxicities were common. Four (6%) patients had grade 3 peripheral neuropathy.

Conclusion mFOLFOX-6 is an active and well-tolerated chemotherapy regimen in advanced adenocarcinoma of stomach/GEJ. This regimen has similar response rates and treatment outcomes with lesser grade 3 or 4 toxicities than that of triplet regimens compared to historical studies.

Keywords

- advanced gastric cancer
- mFOLFOX-6
- palliative chemotherapy

DOI https://doi.org/10.1055/s-0044-1788581 ISSN 2278-330X

How to cite this article: B.P. A, Goel V, Joga S, et al. Efficacy and Safety of mFOLFOX-6 in Advanced Gastric Cancer: A Prospective Observational Study. 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

Introduction

Gastric cancer is one of the common cancers accounting for cancer-related deaths worldwide. It is the 5th most common cancer by incidence and the 4th most common cause of cancer-related deaths worldwide according to GLOBOCAN 2020.[1] The incidence is lower in Indian subcontinent when compared to that of western countries. About two-thirds of the patients with gastric cancer present in advanced stage, and are candidates for palliative treatment alone.[2] These proportions are even higher in the developing countries leading to lower 5-year survival rates.[3] Palliative chemotherapy improves survival and quality of life in patients with metastatic and locally advanced gastric cancers when compared to best supportive care (BSC) alone.[4] Fluoropyrimidines, platinum compounds, taxanes, epirubicin, and irinotecan are the commonly used active drugs in carcinoma stomach. These agents may be employed alone or in combination in first-line therapy. The studies have shown that combination chemotherapy (doublet or triplet) improves survival when compared to single-agent therapy, but at the cost of additional toxicities.[5] The armamentarium for carcinoma stomach is further expanded by the addition of targeted therapies, and more recently by the addition of immunotherapy.[6–9]

There is no single accepted standard chemotherapy regimen for advanced gastric cancers in the first line. The triplet regimens improve response rates, with a significant increase in grade 3/4 adverse effects. Most advanced gastric cancer patients will have difficulty in tolerating such intensive chemotherapy in a palliative setting. So treatment approaches to prolong the life and improve quality of life must consider a careful balance of potential benefits with likely toxicities. Most of the guidelines recommended fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) and a platinum (cisplatin or oxaliplatin) based doublet as the preferred first-line option. So, a doublet chemotherapy is an acceptable treatment choice with comparable response rates and acceptable rates of toxicities. Infusional 5-FU, folinic acid, and oxaliplatin (FOLFOX) doublet is a commonly used chemotherapy regimen in advanced gastric cancers. The scope of this regimen has widened with the recent approval of nivolumab in combination with FOLFOX for advanced gastric cancers in first line.[8] The prospective data on efficacy and safety of FOLFOX in advanced gastric cancer is lacking from the developing countries. So in this prospective observational study, we evaluated the efficacy and toxicity of modified FOLFOX-6 (mFOLFOX-6) in patients with metastatic or locally advanced gastric or gastroesophageal junction (GEJ) adenocarcinomas, as first-line palliative chemotherapy.

Patients and Methods

Patient Eligibility

Eligible adults ($\geq$ 18 years) with histologically proven locally advanced or metastatic adenocarcinoma of stomach/GEJ, who are receiving first-line palliative chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 2, with adequate hematologic, renal, and hepatic functions. Patients were excluded from the study if they are ECOG PS 3 and 4, had coexistent/synchronous malignancies, or had received previous chemotherapy or radiotherapy. Participants had given written informed consent before they entered the study, which was approved by the Ethics Committees of the institute.

Chemotherapy

Patients were administered a mFOLFOX-6 regimen composed of a 2-hour infusion of oxaliplatin (85 mg/m^2) and folinic acid (400 mg/m^2), followed by fluorouracil 400 mg/m^2 intravenous push, then a 46-hour continuous infusion of 5-FU (2,400 mg/m^2). Cycles were repeated every 2 weeks and treatment was continued until disease progression or unacceptable toxicity. Antiemetic prophylaxis was given according to institute protocols.

Response Evaluation

Responses and progression were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) after the completion of four to six cycles. Based on evaluation if it was decided to continue chemotherapy, then the next re-evaluation was done after completion of four to six cycles of additional chemotherapy, followed by every 3 monthly reevaluation until disease progression or death.

Toxicity Assessment

Toxicity was assessed at every visit using the National Cancer Institute Common Toxicity Criteria version 5.0. Peripheral neuropathy was graded according to the following oxaliplatin-specific scale[10]: grade 1: paresthesias/hypoesthesias of short duration with complete recovery before the next cycle; grade 2: paresthesias/hypoesthesias persisting between two cycles without functional impairment; and grade 3: permanent paresthesias/hypoesthesias resulting in functional impairment.

Statistical Analysis

Based on previous studies,[11–13] the response rate to FOLFOX chemotherapy was 30 to 40%. Taking this value as reference, the minimum required sample size with a 15% margin of error and 5% level of significance is 41 patients. Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean $\pm$ standard deviation and median. Kaplan–Meier survival analysis was used to assess progression-free survival (PFS)/overall survival (OS). The log-rank test was used to compare the survival distributions. Statistical significance was defined as $p < 0.05$. The data was entered in MS Excel spreadsheet and analyzed using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

We screened 105 histologically proven patients of carcinoma stomach/GEJ, who were found to be inoperable (locally

advanced) or metastatic at presentation registered at our center. Among them, 39 patients were excluded from the study as the patients did not meet inclusion criteria, mostly due to poor performance status or patients managed with other chemotherapy regimens. Of the 66 patients included in the study, 3 patients were lost to follow-up without a radiologic response evaluation and in one patient the chemotherapy was stopped after one cycle, before any radiological evaluation due to grade 3 cardiotoxicity. At the end of the study, 62 patients were available for final analysis of efficacy. Patient characteristics are listed in ►Table 1.

Efficacy

Sixty-two patients were evaluable for response at least once. Thirty-five (53%) patients had a partial response and none of the patients had a complete response, accounting for an overall response rate (ORR) of 53%. Nineteen (28.8%) had stable disease and 8 (12.2%) patients had progressive disease on first evaluation. The disease control rate (overall response and stable disease) was 81.8%. Sixty-two patients were included in the survival analysis on an intent-to-treat basis. Kaplan–Meier analysis is shown in ►Figs. 1 and 2. The median PFS was 6 months (95% confidence interval [CI] 5.2–6.7 months), and the median OS was 11.5 months (95% CI 9.0–13.9 months). Ascites at presentation and more than one site of metastasis are associated with significantly lower survival on the log-rank test (►Figs. 3 and 4, respectively).

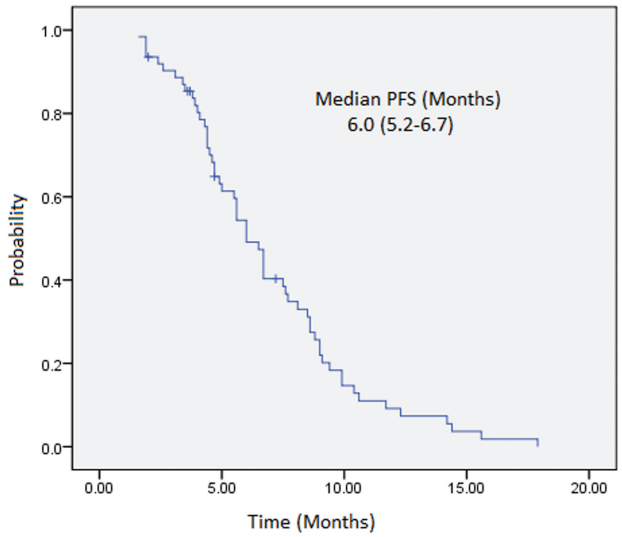

Fig. 1 Kaplan–Meier analysis of progression-free survival.

Safety

A total of 659 cycles of treatment were administered with a median of 10 cycles (range 1–20). The major reason for

Table 1 Patient characteristics

Patient characteristics ($N = 66$)		Number of patients	Percentage (%)
Median age in years		57 (range 20–79)	
Sex	Male	46	60.0
	Female	20	40.0
ECOG PS at presentation	ECOG PS 0	2	3.0
	ECOG PS 1	52	78.7
	ECOG PS 2	12	18.1
Primary site	GEJ	22	33.3
	Cardia/Fundus	3	4.5
	Body	16	24.2
	Antrum/Pylorus	4	6.0
	Linitis plastica	3	4.5
No of metastatic sites	1	30	45.4
	2	20	30.3
	> 2	16	24.2
Site of metastatic disease	Peritoneal	31	46.9
	Ascites	13	19.6
	Liver	17	25.7
	Lung	10	15.1
	Bone	8	12.1
Gastric outlet obstruction	Yes	8	12.1
	No	58	87.9

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEJ, gastroesophageal junction.

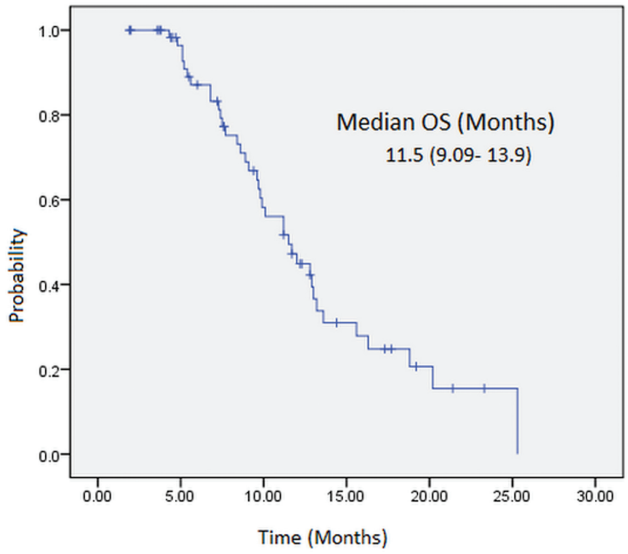

Fig. 2 Kaplan–Meier analysis of overall survival.

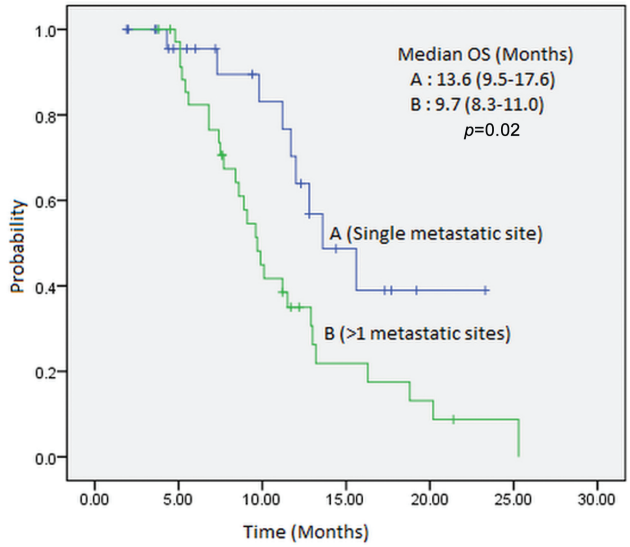

Fig. 4 Number of metastatic sites at presentation as prognostic factor.

discontinuation of chemotherapy was progression of disease. In one patient, chemotherapy had to be discontinued before response evaluation due to grade 3 cardiotoxicity. Eight (12.1%) patients required dose reductions in at least one cycle. Toxicities observed during the treatment are listed in ►**Table 2**. Gastrointestinal and hematological toxicities were predominant, with rates of grade 3/4 nausea/vomiting (13.6%), anemia (15.1%), and neutropenia (13.6%). However, febrile neutropenia was seen in only two patients. Among other toxicities, neurosensory toxicities were the most common. Four (6%) patients had grade 3 peripheral neuropathy.

Discussion

The prognosis of metastatic gastric cancer remains poor despite advances in palliative treatment. Studies comparing combination chemotherapy with BSC only in advanced gastric cancer have consistently shown a survival benefit varying from 3 to 9 months.[14] In a retrospective review of 692 patients on palliative chemotherapy, the median OS of patients who received combination chemotherapy was significantly longer than that of the patients who received single agents (11 vs. 8 months, $p < 0.0001$). The ORRs with various chemotherapy regimens vary from 30 to 70%. In our study, the ORR was 53% (all partial responses) with a disease control rate of 81.8%. The median PFS was 6 months and the median OS was 11.5 months. These results were consistent with the results published in previous studies. In the phase II study by Louvet et al,[15] 49 patients with advanced gastric cancer were treated with FOLFOX and showed an ORR of 44.9% and a median survival of 8.6 months. In another prospective study of mFOLFOX-6, the ORR was 43.8% and the median time to progression and OS were 6.0 months (95% CI, 4.8–7.2 months) and 12.6 months (95% CI, 8.7–16.5 months), respectively.[16] In a phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with Advanced Gastric Cancer (AGC) by Al-Batran et al, 43% of the patients had overall response, and stable disease was observed in 32% of patients. The median OS was 9.6 months. A phase III randomized study by Al-Batran et al,[17] compared fluorouracil, leucovorin plus either cisplatin (FLP) or oxaliplatin (FLO). The median PFS, which was the primary endpoint, was 5.8 months (95% CI, 4.5–6.6 months) and the median OS was 10.7 months (95% CI, 8.5–13.9 months) with FLO. ORR with FLO in the above study was 34.8% and the disease control rate was 75.9%.

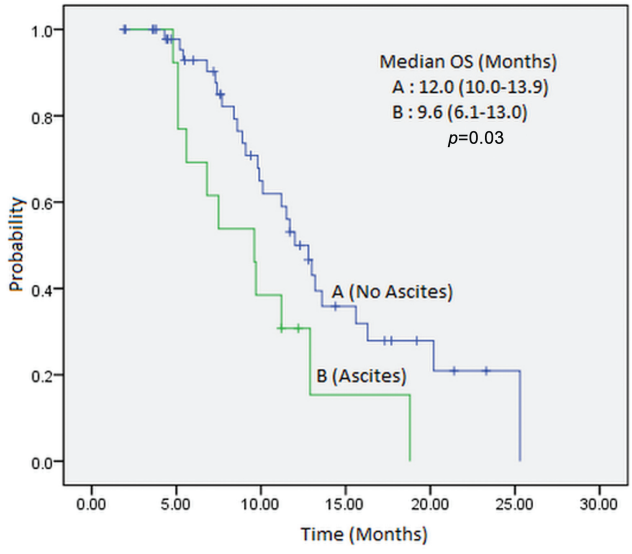

Fig. 3 Ascites at presentation as prognostic factor.

The efficacy of FOLFOX in different studies and their comparison to the present study are presented in ►**Table 3**.

We noticed that the number of metastatic sites at presentation has bearing on PFS/OS. Those patients with single sites of metastasis had significantly better PFS and OS when compared to those with more than one sites of metastasis (median PFS of 8.6 vs. 5.0 months, respectively, $p = 0.05$ and median OS of 13.6 vs. 9.7 months, respectively, $p = 0.02$). The current literature also indicates that malignant ascites at

Table 2 Toxicities associated with the regimen

Toxicity	All grades		Grade 3 or 4	
	No	%	No	%
Hematologic toxicity				
Neutropenia	29	43.9	9	13.6
Thrombocytopenia	24	36.3	5	7.5
Anemia	36	54.5	10	15.1
Gastrointestinal toxicity				
Nausea/vomiting	24	36.3	9	13.6
Diarrhea	21	31.8	6	9.0
Constipation	14	21.2	3	4.5
Stomatitis	11	16.6	2	3.0
Others				
Neurosensory toxicity	29	43.9	4	6.0
Cardiac	2	3.0	1	1.5
Cutaneous	10	15.1	0	0

presentation is associated with poor prognosis in gastric cancer. In a systemic review and meta-analysis, 14 articles including 15 studies, 9 studies assessed the difference in prognosis between patients with and without malignant ascites. A pooled hazard ratio of 1.63 (95% CI: 1.47–1.82, $p < 0.00001$) indicated that gastric cancer patients with malignant ascites had a relatively poor prognosis compared to patients without ascites.[19] Similar findings are also observed in this study.

The mFOLFOX-6 regimen is generally well tolerated and the incidence of grade 3 or 4 toxicities was relatively low even in elderly patients. FOLFOX appear to be well tolerated even in elderly population with similar response rates and comparable toxicity profile. The mFOLFOX regimen resulted in an ORR of 34.9% with a median PFS and OS of 6.8 and 10.5 months, respectively, in a study among elderly patients aged > 70 years.[12] Most of the toxicities are hematological or gastrointestinal, most of them being grade 1 or 2. Neuropathy, a cumulative toxicity of oxaliplatin is a dose-limiting side effect. High rates of oxaliplatin-related neuropathy has been reported with FOLFOX6 in patients with metastatic gastric cancer and FOLFOX-4 in patients with advanced colorectal cancer (21 and 18% grade 3 neurotoxicity, after median cumulative doses of up to 900 mg/m^2).[12,15] However, in the phase 2 study of Al-Batran et al[13] the absence of grade 3 neuropathy is probably related to the low median cumulative dose of oxaliplatin (595 mg/m^2) administered. In our study, four (6%) patients had grade 3 neuropathy requiring dose modifications. A careful watch on neuropathy in patients receiving oxaliplatin and dose modification if required can prevent the debilitating neurological side effects. Fluracil-related cardiac side effects are rare but may be life-threatening. The incidence varies from 0 to 19% in various studies with a wide spectrum of manifestations.[20,21] Only one of our patients had severe chest pain and cardiac dysfunction requiring discontinuation of treatment.

mFOLFOX-6 is an active and well-tolerated chemotherapy regimen in advanced adenocarcinoma of stomach/GEJ. This

Table 3 The efficacy of FOLFOX in different studies with comparison to the present study

Study, year	*N*	Population	Regimen	ORR (%)	PFS (mo	OS (mo)
Louvet et al,[15] 2002	54	All ages	mFOLFOX (100/400/3000)	44.9	6.2	8.6
De Vita et al,[11] 2005	61		FOLFOX 4	38	7.1	11.2
Keam et al,[16] 2008	73	All ages	mFOLFOX6	43.8	6.0	12.6
Al-Batran et al,[13] 2004	37	All ages	FOLFOX (85/500/2600)	43	5.6	9.6
Mohammad et al,[18] 2011	34	All ages	FOLFOX4	53	9.4	12.1
Catalano et al,[12] 2013	43	Elderly, > 70 years	mFOLFOX	34.9	6.8	10.5
Present study	66	All	mFOLFOX-6	53.0	6.0	11.5

Abbreviations: FOLFOX, infusional 5-fluorouracil, folinic acid, and oxaliplatin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

regimen has similar response rates and treatment outcomes with lesser grade 3 or 4 toxicities than that of triplet regimen compared to historical studies. To the best of our knowledge, this is the first prospective study conducted in India for assessing mFOLFOX-6 as a palliative chemotherapy in advanced adenocarcinoma of stomach/GEJ. This study assures the application of western guidelines to current clinical practice in the Indian subcontinent. There is an unmet need to improve outcomes in advanced gastric cancers. Further studies are required for the use of this chemo backbone along with targeted/immunotherapies to improve outcomes of patients with advanced gastric cancer.

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 Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin 2000;50(01):7–33
3 Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2017;8(08):CD004064
4 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
5 Park SC, Chun HJ. Chemotherapy for advanced gastric cancer: review and update of current practices. Gut Liver 2013;7(04): 385–393
6 Bang YJ, Van Cutsem E, Feyereislova A, et al; ToGA Trial Investigators. 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(9742):687–697
7 Shitara K, Bang YJ, Iwasa S, et al; DESTINY-Gastric01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382(25):2419–2430
8 Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398(10294):27–40
9 Wilke H, Muro K, Van Cutsem E, et al; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15(11): 1224–1235
10 Caussanel JP, Lévi F, Brienza S, et al. Phase I trial of 5-day continuous venous infusion of oxaliplatin at circadian rhythm-modulated rate compared with constant rate. J Natl Cancer Inst 1990;82(12):1046–1050
11 De Vita F, Orditura M, Matano E, et al. A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (FOLFOX-4) as first-line treatment of advanced gastric cancer patients. Br J Cancer 2005;92(09):1644–1649
12 Catalano V, Bisonni R, Graziano F, et al. A phase II study of modified FOLFOX as first-line chemotherapy for metastatic gastric cancer in elderly patients with associated diseases. Gastric Cancer 2013;16(03):411–419
13 Al-Batran SE, Atmaca A, Hegewisch-Becker S, et al. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. J Clin Oncol 2004;22(04): 658–663
14 Wöhrer SS, Raderer M, Hejna M. Palliative chemotherapy for advanced gastric cancer. Ann Oncol 2004;15(11):1585–1595
15 Louvet C, André T, Tigaud JM, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 2002;20(23):4543–4548
16 Keam B, Im SA, Han SW, et al. Modified FOLFOX-6 chemotherapy in advanced gastric cancer: results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. BMC Cancer 2008;8:148
17 Al-Batran SE, Hartmann JT, Probst S, et al; Arbeitsgemeinschaft Internistische Onkologie. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26(09):1435–1442
18 Mohammad HA, Magdy FM, Mahmoud OM. FOLFOX (oxaliplatin and 5 fluorouracil/leucovorin) in patients with untreated metastatic gastric adenocarcinoma phase II study. Indian J Cancer 2011;48(04):460–465
19 Zheng LN, Wen F, Xu P, Zhang S. Prognostic significance of malignant ascites in gastric cancer patients with peritoneal metastasis: a systemic review and meta-analysis. World J Clin Cases 2019;7(20):3247–3258
20 Goldberg RM, Sargent DJ, Morton RF, et al. N9741: FOLFOX (oxaliplatin(Oxal)/ 5-fluorouracil (5-FU)/ leucovorin (LV) or reduced dose R-IFL (CPT-11 + 5-FU/LV) in advanced colorectal cancer (CRC): final efficacy data from an intergroup study. JCO 2004;22(14, suppl)3621–3621
21 Sara JD, Kaur J, Khodadadi R, et al. 5-fluorouracil and cardiotoxicity: a review. Ther Adv Med Oncol 2018;10:1758835918780140

