OUTCOME OF FOLFOX AND MODIFIED DCF CHEMOTHERAPY REGIMEN IN PATIENTS WITH ADVANCED GASTRIC ADENOCARCINOMA

Mehdi Pourghasemian, Amin Danadeh Mehr, Mohammad Molaei, Afshin Habibzadeh*

Abstract

Objectives: Chemotherapy is used as an indispensable therapy for advanced gastric cancer. Different chemotherapy regimens have been used for this purpose. Toxicity due to the chemotherapy drugs is one limiting factor. In this study we aim to compare the efficacy and toxicity of two regimens FOLFOX (leucovorin, 5-fluorouracil and oxaliplatin) and modified DCF (mDCF) (docetaxel, cisplatin, and 5-fluorouracil) in patients with advanced gastric adenocarcinoma.

Methods: In this analytical cross-sectional study, 47 patients treated with FOLFOX regimen and 57 patients treated with mDCF regimen were recruited. Patients in both groups were compared for demographic findings, response rate, mortality rate, overall survival (OS) and progression free survival (PFS).

Results: In FOLFOX and mDCF group, complete response (CR) occurred in 4.3% and 5.3%, partial response (PR) in 42.6% and 29.8%, stable disease in 34% and 52.6% and disease progression in 19.1% and 12.3%, respectively (p=0.25). Overall response rate was 48.9% and 56.1%, respectively. There was no significant difference between two regimens in OS and PFS (p=0.22). mDCF compared to FOLFOX had significantly higher hematologic, gastrointestinal complications, as well as creatinine rise, stomatitis and hair loss, but peripheral neuropathy was significantly lower.

Conclusion: The results of current study showed that in patients with advanced gastric adenocarcinoma, FOLFOX regimen compared to mDCF regimen have similar ORR, OS and PFS. Toxicity rate are also lower in FOLFOX group, thus it seems a better regimen for chemotherapy.

Keywords: Advanced gastric adenocarcinoma- FOLFOX- modified DCF- survival rate- toxicity

Introduction

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related death in the world (Ferlay et al., 2015; Haghighi et al., 2016). Approximately two-thirds of these cancers occur in the developing countries in Eastern Europe, South America, and Asia (Chen et al., 2014). In Iran, gastric cancers are the most common cause of cancer deaths and their incidence are higher than the global average (Zamani et al., 2013).

Surgery is the only definitive cure for gastric cancer, but a significant proportion of these patients are at the advanced stage at the time of diagnosis, or more than half develop recurrence after surgery. Therefore palliative chemotherapy is now a well-known and effective method compared to other supportive treatments in patients with advanced gastric cancer (Huang et al., 1998; Zabaleta, 2012).

The overall survival (OS) of advanced gastric cancer is very low; the median OS was 7.5 to 12 months after chemotherapy compared with 3 to 5 months in patients receiving supportive therapy. Although overall treatment outcomes have not been satisfactory, chemotherapy has been associated with higher survival and better quality of life compared to supportive treatment (Casaretto et al., 2006; Glimelius et al., 1997; Wagner et al., 2006; Wagner et al., 2010). In addition, meta-analysis studies have shown that combination therapy is also highly effective (Iwase et al., 2011; Koizumi et al., 2012; Kim et al., 2011) and the triple-drug regimen is much better than the single-drug or double-drug regimen (Koizumi et al., 2008; Van Cutsem et al., 2006).

Different chemotherapy regimens have been introduced for patients with advanced gastric cancer. Oxaliplatin plus 5-fluorouracil (5-FU) and leucovorin, as FOLFOX regimen, is widely used in the treatment of gastrointestinal cancers with 40-50% response rate and survival after treatment to be 10 to 12 months (Oh et al., 2007). Docetaxel plus cisplatin plus 5-FU as the DCF regimen is the other commonly used regimen which has been associated with acceptable survival and better quality of life (Chen et al., 2013).

Despite the efficacy of DCF in progressive gastric cancer, studies have reported that the incidence of grade...
3-4 chemotherapy related toxicities is higher than other combination regimens and is therefore not the standard treatment regimen in these patients (Roth et al., 2007; Van Cutsem et al., 2006). However, FOLFOX had acceptable anti tumor activity and tolerable toxicity profile in different treatment protocols and doses (Hacibeikiroglu et al., 2015; Haghighi et al., 2016; Yeh et al., 2012; Zhang et al., 2012).

The aim of our study was to evaluate the efficacy of FOLFOX as the first line of treatment in patients with advanced gastric adenocarcinoma compared with mDCF.

Materials and Methods

In this cross-sectional study, all patients between 18-80 years old with advanced gastric adenocarcinoma (non-resectable tumor) receiving FOLFOX-4 or modified DCF chemotherapy regimen during October 2015 and October 2018 were included. Patients with previous history of chemotherapy or other malignancy, severe underlying or infectious disease, with brain metastasis or other causes of severe neuropathy were excluded. The ethics committee of Ardabil University of Medical Sciences have approved the study protocol (Approve no: ARUMS.REC.1396.209).

In all patients, demographic and baseline data including age at the time of diagnosis, gender, clinical findings, disease stage and metastasis as well as demographic, physical exam, laboratory and imaging findings at the end of each chemotherapy cycles were recorded.

Tumor was evaluated using CT studies every four cycles. Patients response to treatment was measured by RECIST criteria (Response Evaluation Criteria In Solid Tumors) using http://www.radiologytutor.com/index.php/cases/oncol/139-recist. CT scan findings were compared before chemotherapy and after each period to define RECIST.

Complete remission (CR) was defined as there was no sign of disease, Partial response (PR) is considered when at least 30 percent of tumor mass was reduced in imaging studies and there was no new lesion or findings regarding the disease progress. Progressive disease (PD) was noted if there was at least 20% increase in largest diameter of the lesion or occurrence of new lesion or metastasis. Stable disease was considered when the treatment response did not reach any criteria of complete or partial response and also is not progressive. Overall response rate (ORR) was the sum of PR and CR.

Progress free survival (PFS) was the duration from the diagnosis of the disease till the recurrence or disease progress or the patient death. Those patients with no changes during the study period were excluded from this evaluation.

The chemotherapy related complications including hematologic, gastrointestinal, neuropathy were recorded in both treatment groups. We also evaluated other drug-related complications.

Statistical analysis

All data were analyzed using the SPSS software 20 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, U.S.A.). Results were presented as mean and standard deviation (SD) or frequency and percentage. Independent T test or Mann Whitney U, Chi square of Fischer’s exact tests were used to compare the findings between two regimens. P-values of <0.05 were considered significant.

Results

In this study, 104 patients received chemotherapy including 47 with FOLFOX regimen and 57 with mDCF. There was no difference between groups regarding baseline findings (Table 1).

Figure 1 is demonstrating the response rate between groups. mDCF compared to FOLFOX had more cases with stable disease and less progression, but there was no significant difference between groups (p=0.25). ORR was 46.98% in FOLFOX and 35.1% in mDCF, but the difference was not significant (p=0.22).

Six patients (12.8%) in FOLFOX group and 10 patients (17.5%) in mDCF group died during the study period (p=0.5). The time between disease diagnosis and death in these patients were 8.33±1.03 months in FOLFOX vs. 6.50±2.32 months in mDCF group (p=0.09).

Overall survival (OS) in FOLFOX and mDCF groups were 12.61±4.05 and 13.50±5.94 months, respectively with no significant difference between groups. FOLFOX

Figure 1. Response Rate between FOLFOX and mDCF Groups
compared to mDCF groups had shorter PFS with no significant difference between groups (6.79±2.18 vs. 7.97±3.14, p=0.1).

Chemotherapy related toxicities are demonstrated in Table 2. Hematologic complications including neutropenia, fever and neutropenia and thrombocytopenia were significantly higher in mDCF compared to FOLFOX group. mDCF compared to FOLFOX regimen had significantly more cases with post-chemotherapy nausea and vomiting, creatinine rise, hair loss and facial changes (in all patients) and stomatitis. Neuropathy occurred in both groups in significantly higher incidence in FOLFOX compared to mDCF regimen. Most cases of neuropathy in both groups were grade I and II.

Discussion

In this retrospective cross-sectional study, we evaluated the outcome of patients with advanced gastric adenocarcinoma following treatment with FOLFOX or mDCF regimens.

The FOLFOX group had a relatively equal CR rate, higher PR, greater disease progression and lower stable disease compared with mDCF. Also, the ORR between the two groups was not statistically significant, despite being higher in the FOLFOX group.

Haghighi and colleagues (2016) in their study of elderly patients with advanced gastric cancer treated with FOLFOX-4, observed ORR of 72.6% with stable disease in 13%. In another study of elderly patients, Liu et al., (2008) observed that treatment with FOLFOX-4 was associated with an ORR of 52.5%. In the study of Yeh et al., (2012) the OR was 41.1%, the disease was stable in 11.9 months in Yeh et al., study (2012). However, Baek et al., (2011) reported lower rate of OS and PFS (9.3 and 4.9 months, respectively).

In the current study, FOLFOX-4 regimen had OS of 12 months and PFS of 6.7 months, with OS and PFS equal to some studies. Chen and colleagues (2013) concluded that the DCF regimen increases PR levels and reduced disease progression. Wang et al. (2016) reported ORR of 48.7% following treatment with DCF in Chinese patients.

Hacibekiroglu et al., (2015) reported rather similar efficacy for FOLFOX-6 and DCF in advanced gastric cancers (OR of 37% and 40.3%, respectively). Kim et al., (2011) also noted that both FOLFOX and DCF regimens have similar improvement rate. Also, in our study both regimens have relatively equal efficacy.

In the present study, FOLFOX-4 regimen had OS of 12 months and PFS of 6.7 months, with OS and PFS equal to some studies (Haghighi et al., 2013; Liu et al., 2008; Yeh et al., 2012). For FOLFOX-4 regimen, Haghighi et al., (2013) reported OS of 11.9 and PFS of 7.3; the mean OS in the study of Liu et al., (2008) was 10 months 11.9 months in Yeh et al., study (2012). However, Baek et al., (2011) reported lower rate of OS and PFS (9.3 and 4.9 months, respectively).

In the current study, Mortality was seen in 12.8% and 17.5% of FOLFOX-4 and modified DCF groups. There was no significant difference between two regimens regarding PFS and OS rate, while the PFS was lower in FOLFOX group.

Similar to our study, Hacibekiroglu et al., (2015) also found that the both FOLFOX and DCF had relatively similar survival rates. However, Kim et al., (2011) reported shorter duration of disease progression for DCF compared to FOLFOX (4 vs. 15 months) with longer OS (48 vs.

Table 1. Baseline Findings in FOLFOX and mDCF Groups

|                     | FOLFOX       | Modified DCF | P value |
|---------------------|--------------|--------------|---------|
| Age (years)         | 65.87±12.74  | 63.07±9.27   | 0.19    |
| Gender              |              |              |         |
| Male                | 33 (70.2%)   | 46 (80.7%)   | 0.21    |
| Female              | 14 (29.8%)   | 11 (19.3%)   |         |
| Stage               |              |              |         |
| III                 | 15 (31.9%)   | 20 (35.1%)   | 0.73    |
| IV                  | 32 (68.1%)   | 37 (64.9%)   |         |
| Metastasis          |              |              |         |
| Liver               | 12 (25.5%)   | 17 (29.8%)   | 0.99    |
| Abdomen and peritoneum | 10 (21.3%) | 7 (12.3%)   |         |
| Lung                | 3 (6.4%)     | 2 (3.5%)     |         |
| More than one Organ | 7 (14.9%)    | 11 (19.3%)   |         |

Table 2. Chemotherapy Related Toxicities between FOLFOX and mDCF Groups

|                     | FOLFOX       | Modified DCF | P value |
|---------------------|--------------|--------------|---------|
| Hematologic complications | 12 (25.5%) | 41 (71.95)   | <0.001  |
| Neutropenia         | 9 (19.1%)    | 37 (64.9%)   | <0.001  |
| Fever and neutropenia | 2 (4.3%)   | 19 (33.3%)   | <0.001  |
| Thrombocytopenia    | 5 (10.6%)    | 19 (33.3%)   | 0.006   |
| Gastrointestinal complications | 19 (40.4%) | 37 (64.9%)   | 0.01    |
| Diarrhea            | 5 (10.6%)    | 19 (33.3%)   | 0.006   |
| Nausea              | 12 (25.5%)   | 35 (61.4%)   | <0.001  |
| Vomiting            | 9 (19.1%)    | 29 (50.9%)   | <0.001  |
| Increase in liver enzymes | 2 (4.3%)   | 8 (14%)      | 0.09    |
| Creatinine rise     | 5 (10.6%)    | 15 (26.3%)   | 0.04    |
| Stomatitis          | 1 (2.1%)     | 20 (35.1%)   | <0.001  |
| Hair loss           | 2 (4.3%)     | 57 (100%)    | <0.001  |
| Neuropathy          | 27 (57.4%)   | 9 (15.8%)    | <0.001  |
| Neuropathy grade    |              |              |         |
| I                   | 14 (29.8%)   | 6 (10.5%)    | <0.001  |
| II                  | 10 (21.3%)   | 5 (10%)      |         |
| III                 | 2 (4.3%)     | 0            |         |
| IV                  | 1 (2.1%)     | 0            |         |
in advanced gastric cancer patients. However, Liu et al., (2018) observed that DOF regimen (Oxaliplatin instead of cisplatin) compared to FOLFOX regimen was more effective in advanced gastric cancer patients.

Chemotherapy-related toxicities are one of the causes that limit the use of different chemotherapy regimens. Therefore, researchers are trying to introduce regimens that have the least or acceptable toxicity with higher efficiency. The DCF regimen has higher rate of grade 3-4 toxicities than other therapies and so has limited its use (Roth et al., 2007; Van Cutsem et al., 2006).

In our study, hematologic and gastrointestinal complications were significantly higher in modified DCF, while peripheral neuropathy was significantly higher in FOLFOX-4. In other studies, the FOLFOX regimen was more acceptable due to its lower chemotherapy-related toxicities. Haghighi et al., (2016) reported only one case of grade 3 neuropathy in FOLFOX group.

Similar to the present study, Hacibekiroglu et al., (2015) reported higher hematologic and gastrointestinal toxicities in DCF compared to FOLFOX regimen. Similarly, Kim et al., (2011) stated that mucositis grade 3-4 and leukopenia were more frequent in patients treated with DCF. Unlike these findings, Liu et al., (2018) observed that both DOF and FOLFOX regimen have acceptable toxicities comparable with each other, but in elderly patients, DOF has significantly more neuropathy.

Stomatitis is another chemotherapy-related complication which was significantly higher in mDCF compared to FOLFOX. Similar results were reported by Wang et al., (2014), while Hacibekiroglu et al., (2015) did not find significant difference in stomatitis rate between groups. Salehifar et al., (2019) also find no significant difference between two groups in stomatitis, visual change and skin reactions.

Another notable finding was hair loss in 100% of mDCF patients, which was seen in only 4.3% of FOLFOX patients. Bhat (2018) also reported less hair loss in similar FOLFOX regimen compared to others. This hair loss and change in the appearance can have a significant impact on the morale and cause depression in these patients.

Mitani et al., (2020) also indicated that FOLFOX6 has acceptable toxicity for chemotherapy-refractory advanced gastric cancer. Given the sum of the side effects of the treatment and the resulting toxicities, a treatment should be chosen that is well-tolerated with lower complications.

In conclusion, the results of current study showed that in patients with advanced gastric adenocarcinoma, FOLFOX regimen compared to mDCF regimen have similar ORR, OS and PFS. Toxicity rate are also lower in FOLFOX group, thus it seems a better regimen for chemotherapy.

Acknowledgments

The present study was extracted from the thesis written by Dr. Mohammad Molaei which was financially supported by Ardabil University of Medical Sciences. Authors declared no conflict of interest.

References

Back YH, Choi SR, Jang JS, et al (2011). Modified FOLFOX-4 as first-line and salvage treatment in advanced gastric cancer. Hepatogastroenterology, 58, 251-6.

Bhat G (2018). Retrospective study of oxaliplatin, leucovorin and 5 fluorouracil regimen in patients with advanced gastric cancer with poor performance status: A study at a tertiary center of South India. South Asian J Cancer, 7, 223-5.

Casaretto L, Sousa PL, Mari JJ (2006). Chemotherapy versus support cancer treatment in advanced gastric cancer: a meta-analysis. Braz J Med Biol Res, 39, 431-40.

Chen W, Shen J, Pan T, et al (2014). FOLFOX versus EOX as a neoadjuvant chemotherapy regimen for patients with advanced gastric cancer. Exp Ther Med, 7, 461-7.

Chen X-L, Chen X-Z, Yang C, et al (2013). Docetaxel, cisplatin and fluorouracil (DCF) regimen compared with non-taxane-containing palliative chemotherapy for gastric carcinoma: A Systematic Review and Meta-Analysis. PLoS One, 8, e60320.

Ferlay J, Soerjomataram I, Dikshit R, et al (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer, 136, 359-86.

Funasaka C, Kanemasa Y, Shimoyma T, Cho H, Omuo Y (2020). Clinical efficacy of mFOLFOX6 for advanced gastric cancer. Gan To Kagaku Ryoho, 47, 49-53.

Glimelius B, Ekstrom K, Hoffman K, et al (1997). Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol, 8, 163–8.

Hacibekiroglu I, Kodaz H, Erdogan B, et al (2015). Comparative analysis of the efficacy and safety of oxaliplatin plus 5-fluorouracil/leucovorin (modified FOLFOX6) with cisplatin and fluorouracil (DCF) regimen compared with DCF. Eur J Cancer, 51, 40-9.

Haghighi S, Kashekar H, Esmaeilpour K, et al. (1997). Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol, 8, 163-8.

Hayashi K, Kadohara T, Tsunoda Y, et al (2016). Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX4) as first line chemotherapy in elderly patients with advanced gastric cancer. Asian Pac J Cancer Prev, 16, 2355-9.

Hacibekiroglu I, Kodaz H, Erdogan B, et al (2015). Comparative analysis of the efficacy and safety of modified FOLFOX-6 and DCF regimens as first-line treatment in advanced gastric cancer. Mol Clin Oncol, 3, 1160-4.

Haghighi S, Kashekar H, Esmaeilpour K, et al. (2016). Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX4) as first line chemotherapy in elderly patients with advanced gastric cancer. Asian Pac J Cancer Prev, 17, 3277-80.

Huang QJ, Sridhar S, Chen Y, et al (1998). Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. Gastroenterology, 114, 1169-79.

Iwase H, Shimada M, Tsuchiya T, et al (2011). A phase II multicenter study of triple therapy with paclitaxel, S-1 and cisplatin in patients with advanced gastric cancer. Oncology, 80, 76-83.

Kim JY, Do YR, Park KU, et al (2011). Multicenter phase II trial of S-1, paclitaxel and cisplatin triplet combination chemotherapy in patients with advanced gastric cancer. Cancer Chemother Pharmacol, 67, 527-32.

Kim YJ, Gob PG, Kim ES, et al (2011). Comparison of the toxicities and efficacies of the combination chemotherapy regimens in advanced gastric cancer patients who achieved complete response after chemotherapy. Korean J Gastroenterol, 58, 311-7.

Koizumi W, Nakayama T, Tanabe S, et al (2012). A multicenter
phase II study of combined chemotherapy with docetaxel, cisplatin, and S-1 in patients with unresectable or recurrent gastric cancer (KDOG 0601). *Cancer Chemother Pharmacol*, **69**, 407–13.

Liu ZF, Guo QS, Zhang XQ, et al (2008). 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. *Am J Clin Oncol*, **31**, 259-63.

Liu M, Hu G, Wang Y, et al (2018). Comparison of FOLFOX and DOF regimens as first-line treatment in East Asian patients with advanced gastric cancer. *Oncol Targets Ther*, **11**, 375-81.

Mitani S, Kadowaki S, Komori A, et al (2020). A phase II study of modified FOLFOX6 for advanced gastric cancer refractory to standard therapies. *Adv Ther*, **37**, 2853-64.

Oh SY, Kwon HC, Seo BG, et al (2007). A phase II study of oxaliplatin with low dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) as first line therapy for patients with advanced gastric cancer. *Acta Oncol*, **46**, 336–41.

Roth AD, Fazio N, Stupp R, et al (2007). 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*, **25**, 3217-23.

Salehifar E, Avan R, Jambabaei G, Mousavi SK, Faramarzi F (2019). Comparison the incidence and severity of side effects profile Of FOLFOX and DCF regimens in gastric cancer patients. *Iran J Pharm Res*, **18**, 1032-9.

Van Cutsem E, Moiseyenko VM, Tjulandin S, et al (2006). 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*, **24**, 4991–7.

Wagner AD, Grote W, Haerting J, et al (2010). Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev*, **3**, CD004064.

Wagner AD, Unverzagt S, Grote W, et al (2010). Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev*, **3**, CD004064.

Van Cutsem E, Moiseyenko VM, Tjulandin S, et al (2006). 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*, **24**, 4991–7.

Wagner AD, Grote W, Haerting J, et al (2006). Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol*, **24**, 2903–9.

Wagner AD, Unverzagt S, Grote W, et al (2010). Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev*, **3**, CD004064.

Wang J, Xu R, Li J, et al (2016). Randomized multicenter phase III study of a modified docetaxel and cisplatin plus fluorouracil regimen compared with cisplatin and fluorouracil as first-line therapy for advanced or locally recurrent gastric cancer. *Gastric Cancer*, **19**, 234-44.

Yeh YS, Tsai HL, Ma CJ, et al (2012). A retrospective study of the safety and efficacy of a first-line treatment with modified FOLFOX-4 in unresectable advanced or recurrent gastric cancer patients. *Chemotherapy*, **58**, 411-8.

Zabaleta J (2012). Multifactorial etiology of gastric cancer. *Methods Mol Biol*, **863**, 411-35.

Zamani N, Hajifaraji M, Fazel-tabar Malekshah A, et al (2013). A case-control study of the relationship between gastric cancer and meat consumption in Iran. *Arch Iran Med*, **16**, 324-9.

Zhang J, Chen RX, Zhang J, et al (2012). Efficacy and safety of neoadjuvant chemotherapy with modified FOLFOX7 regimen on the treatment of advanced gastric cancer. *Chin Med J (Engl)*, **125**, 2144-50.

This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.