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A Phase II Study on Triple Chemotherapy (DOX) in Patients with Advanced Gastro-Esophageal Adenocarcinoma

Dr.Tshetiz Dahal (MBBS)
General Physician/Clinical Researcher and Writer
Lugansk State Medical University
Luhansk Oblast, 93000 Luhansk, Ukraine

Contact: +91 8617009714 & +380 506266617 / Email: dahaltshetiz21@gmail.com
Twitter : @DrTshetiz / ORCID ID : https://orcid.org/0000-0002-4042-7768

ABSTRACT

Advanced gastro-esophageal (GE) cancer patients who get triple chemotherapy have improved outcomes. I determined a recommended dose of triple chemotherapy using docetaxel (D), oxaliplatin (O), and capecitabine (X) in a phase I dose-finding experiment with 23 patients (DOX). We saw encouraging activity, and in the next phase II trial, we offer efficacy data. Patients and Procedures All patients had GE adenocarcinoma, which was histologically verified. The first day of treatment included infusions of docetaxel (51 mg/m2 for 60 minutes), oxaliplatin (100 mg/m2 for 30 minutes), and capecitabine (1250 mg/m2/day continuously). Treatment was continued every three weeks until the condition progressed or the toxicity became intolerable. RECIST 1.0 and NCIC-CTC 3.0 were used, respectively, to evaluate toxicity and response. Results: 42 individuals with metastatic illness and a median age of 64 years were included. An investigator-evaluated response rate of 66 percent was achieved by six patients (14%), 22 patients (52%), and 22 patients, respectively. Overall survival was 11.8 months, with a median progression-free survival of 7.7 months. Twenty patients were found to have neutropenia grades 3 and 4. (total 48 percent). Fourteen patients had febrile neutropenia (33 percent). There were six DOX on average. In patients with advanced GE cancer, DOX (D: 51 mg/m2 day 1, O: 100 mg/m2 day 1, and X: 1250 mg/m2) continuously every 3 weeks can be provided in an outpatient setting. The efficacy is extremely encouraging and merits examination in larger trials.

INTRODUCTION

The second most prevalent cause of cancer-related fatalities globally and the fourth most frequent kind of malignancy, respectively, are stomach and esophageal cancers [1]. Patients with advanced gastro-esophageal adenocarcinomas (aGEA) still have a very bad prognosis, despite the fact that treatment has become a little more aggressive lately. A meta-analysis also revealed a significant and persistent survival advantage for combination chemotherapy compared to single-agent treatment, and other trials have proven that combination chemo-regimens resulted in a higher response rate (RR) than monotherapy [2,3]. The cornerstones of treatment for aGEA are fluoropyrimidine- and platinum-based treatments. According to various studies, capecitabine (X) and oxaliplatin (O) can both replace fluorouracil (F) and cisplatin (C), reducing adverse effects and simplifying treatment for out-patients [4,5]. The REAL-2 experiment [4] looked at several chemotherapy setups. Epirubicin (E), cisplatin, and 5-FU were selected as the control arm, and in a 2 2 factorial design, cisplatin was replaced by oxaliplatin and fluorouracil by oral capecitabine. The authors discovered that capecitabine and oxaliplatin were non-inferior in the two-by-two comparison (primary endpoint), but that the EOX group had a longer overall survival (OS) than the ECF group, with a median OS of 11.2 months. A number of cancer trials have since validated the effectiveness of capecitabine and oxaliplatin [6, 7]. Furthermore, research indicated that triple chemotherapy enhances efficacy in aGEA patients. In comparison to doublet combinations, the addition of an anthracycline or taxane to platinum and a fluoropyrimidine increases RR and modestly improves OS, but it also exposes patients to more severe side effects [2,3,8,9]. Patients in the V-325 trial [8] received cisplatin and fluorouracil as a first-line treatment, either with or without docetaxel. Docetaxel was added to increase RR, progression-free survival (PFS), and two-year overall survival (OS). The effectiveness of taxanes has been supported by numerous studies and meta-analyses [2,10–13], and the most promising regimen at the moment is a triple combination of taxanes, albeit the ideal schedule has not yet been determined. Numerous modified regimens have been created in light of the substantial toxicities connected with the triple taxane-containing regimen. We developed a recommended dose of triple chemotherapy with docetaxel, short-term infusion of oxaliplatin, and continuously

capecitabine in a phase I dose discovery trial with 23 patients [14]. (DOX). We saw encouraging activity, and in the next phase II trial, we offer efficacy data.

PATIENTS AND METHODS

All patients had to have lower esophageal adenocarcinoma, gastro-oesophageal junction cancer, or stomach cancer with histological confirmation and not be candidates for surgical resection. Other requirements for inclusion included measurable disease as determined by RECIST 1.0, WHO performance status (WHO PS) 0-1, age of 18 or older, no history of chemotherapy other than adjuvant chemotherapy that was finished at least six months prior to inclusion, adequate bone marrow function (neutrophils count > 1.5 109/l; platelets > 100 109/l), adequate hepatic function (serum bilirubin 1.5 upper normal limit (UNL), Additionally, the treatment must begin within eight days of the patient's inclusion, and the patient must have peripheral neuropathy, another serious medical condition that coexists with it, show signs of brain metastases, or be receiving concurrent treatment with another anticancer medication. Females who were pregnant or nursing were excluded.
The LSMU Health Authority and the local ethics committee both gave their approval to the study. Before participating in the trial, all patients provided their signed informed consent.

TREATMENT SCHEDULE

According to the advice from our phase I study, treatment was started with docetaxel (60 mg/m2 as a 60-minute infusion day 1), oxaliplatin (115 mg/m2 as a 30-minute infusion day 1), and capecitabine (1250 mg/m2/day continuously) [14]. We modified the phase II protocol and reduced the doses of docetaxel and oxaliplatin by 15% each, to 51 mg/m2 and 100 mg/m2, respectively, in order to maintain treatment cadence without dose decreases and, ideally, with less toxicity [15]. After 12 patients received the increased dose of DOX, the new recommendation was modified, authorized by the regional ethics council, and implemented. For an intended eight cycles, DOX was repeated every three weeks.

ASSESSMENTS

Each patient underwent a thorough physical examination, a complete blood count, a clotting profile, blood biochemistry, a 12-lead electrocardiogram, a contrast-enhanced CT scan of the thorax, abdomen, and pelvis, as well as a pregnancy test for women who were able to become pregnant, all of which were performed prior to inclusion. Before the start of each cycle, a thorough physical examination, blood biochemistry analysis, and an evaluation of toxicity and adverse events were repeated; a complete blood count was also performed before each docetaxel infusion. Only patients who tested negative for HER2 starting in May 2010 were included. At the conclusion of every third treatment cycle until disease progression, a tumour marker evaluation and contrast-enhanced CT scan of the thorax, abdomen, and pelvis were performed once more. The researcher assessed the response using RECIST 1.0 for each. Toxicity was evaluated according to NCIC-CTC 3.0.

STUDY END-POINTS

The study's main clinical endpoint was RR. OS, PFS, treatment-related toxicity, and disease-related symptoms were considered secondary endpoints. PFS was outlined as the period of time from enrollment to the occurrence of progressive illness (as measured by the RECIST criteria) or death from any cause. OS was outlined as the period of time from inclusion and mortality from any cause. On December 1st, 2020, data was updated.

STATISTICAL ANALYSES

The use of non-parametric statistics was made. The range included in brackets is shown after each median value. Patients who did not show evidence of progress after treatment was stopped underwent clinical and radiological examination every three months. Based on Simons two-stage concept, there are a certain number of evaluable patients [16]. The Kaplan-Meier method was used to produce PFS and OS. A Medlogdatabase was used to store and analyse the data. An intention-to-treat population was used for all analyses.

RESULTS

Patients Characteristics

Table 1 summarizes baseline demographic and patient characteristics. 42 patients were included between September 2009 and September 2012, with a median age of 64 years (IQR 44–76) and WHO PS scores of 0 and 1 in 57% and 43%, respectively, in the population that was intended to be treated. In 12 individuals, the lower oesophagus, in 23, the gastro-oesophageal junction, and in 7, the stomach, the primary tumour location. All of the patients had metastatic (n = 3) or locally advanced illness that was incurable.

TABLE-1: Baseline characteristics for 42 patients with advanced gastro-esophageal adenocarcinoma treated with DOX.

Number of patients	**42**
Age, years	
Median	64
Range	44-76
Sex	
Male	36 (86%)
Female	6 (14%)
WHO performance status	
0	24 (57%)
1	18 (43%)
Primary tumour site	
Esophagus	12 (28%)
GEJ	23 (55%)
Stomach	7 (17%)
Status of primary tumour	
R0 resection	5 (12%)
R2 resection	1 (2%)
No surgery	36 (86%)
No patient had prior CT or RT	
Stage	
Locally advanced	3 (7%)
Metastatic	39 (93%)
No. of organs involved	
1	2 (5%)
2	14 (36%)
3	14 (36%)
≥ 4	9 (23%)
Increased	
Alkaline phosphatase (> 300 U/l)	4 (10%)
ALAT (> 40 U/l)	6 (14%)
Platelets (> 400 × 109 /l)	14 (33%)
ANC (> 7.5 × 109 /l)	22 (52%)

ADMINSTERED TREATMENTS

252 cycles were administered overall throughout the research, with a median of 6 cycles administered to each patient (IQR 4-8). Docetaxel and oxaliplatin had cumulative dosages of 308 mg/m2 and 426 mg/m2, respectively. Docetaxel and oxaliplatin had median relative dosage intensities (RDI) of 0.97 and 0.96, respectively. PD (n = 11.26%), toxicity (n = 17.41%), and completion of planned therapy (n = 14.33%) were the causes of study treatment cessation. Table 2 displays the treatments that were given.

TABLE-2: Efficacy data and dose administration for 42 patients with advanced gastro-esophageal adenocarcinoma treated receiving DOX.

Number of patients	**42**
Efficacy	
Complete response (CR), n (%)	6 (14%)
Partial response (PR), n (%)	22 (52%)
Disease control (CR + PR + NC*), n (%)	35 (83%)
PFS, months (median)	7.7 (5.5-9.7)
OS, months (median)	11.8 (7.6-15.2)
Reason for discontinuation of DOX	
Completed planned number of DOX	14 (33%)
Progressive Disease	11 (26%)
Toxicity or patients wish	17 (41%)
Dose administration	
Number of DOX (median, IQR)	6 (4-8)
Number of docetaxel cycles (median, IQR)	6 (4-8)
Cumulative dose of D, (median, IQR)	308 (204-350)
Dose intensity of D	97 (94-100)
Cumulative dose of O, (median, IQR)	426 (305-592)
Dose intensity of O, (median, IQR)	96 (82-100)
Duration of therapy, months (median, IQR)	4.8 (3.0-5.5)

***NC = No Change**

TOXICITY

In general, the treatment was favourably received. Twenty patients (or 48%) had grade 3 or 4 neutropenia, but there was no evidence of grade 3 or 4 thrombocytopenia. Only 6 of 30 patients (20%) experienced febrile neutropenia after the 15% dose reduction of docetaxel and oxaliplatin, compared to 8 of 12 patients (66%) who got high dose DOX. Table 3 displays the occurrence rates of haematological and non-hematological adverse events. The most significant grade 3 and grade 4 non-hematologic effects were neuropathy (17%), diarrhoea (14%), fatigue (12%), and nausea (7%).

TABLE-3: Worst toxicity for 42 patients with advanced gastro-esophageal adenocarcinoma treated receiving DOX.

Hematologictoxicity	**Grade II n (%)**	**Grade III n (%)**	**Grade IV n (%)**
Neutropenia	3 (7%)	10 (24%)	10 (24%)
Thrombocytopenia	0	0 (0%)	0 (0%)
Febrile neutropenia	-	13 (31%)	1 (2%)
Non-hematologic toxicity	**Grade II n (%)**	**Grade III n (%)**	**Grade IV n (%)**
Nausea	8 (19%)	3 (7%)	0
Diarrhoea	6 (14%)	6 (14%)	0
Vomit	4 (10%)	1 (2%)	0
Neuropathy	13 (31%)	7 (17%)	0
Fatigue	23 (55%)	5 (12%)	0
Nail toxicity	13 (31%)	5 (12%)	-
HFS	8 (19%)	3 (7%)	-
Anorexia	3 (7%)	2 (5%)	-

In addition one patient had pulmonary embolism after the 6th cycle of DOX.

EFFICACY

The response rate was 66% (6 patients obtained complete response (CR) and 22 patients obtained partial response (PR)) and disease control rate was 83% (Table 2). Median PFS and OS were 7.7 months; 95% CI 5.5-9.7 months and 11.8 months; 95% CI 7.6-15.2 months, respectively (Figure 1). Three patients with locally advanced disease died after 2, 15 and 29 months, respectively. There was no sign of difference in efficacy (RR, PFS or OS) between patients receiving the initial higher dose of DOX and the recommended adjusted DOX.

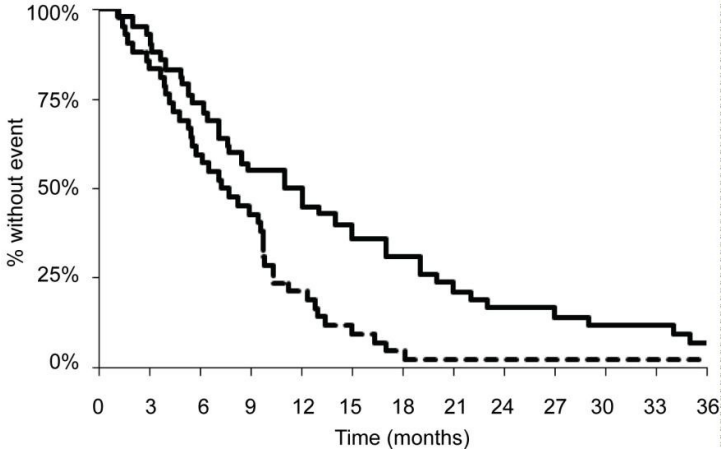

FIGURE 1 : Kaplan-Meier survival curve demonstrating progression-free survival (dotted line) and overall survival (solid line). Kaplan-Meier curves of progression-free survival (median 7.7 months; 95% CI 5.5-9.7 months), dotted line, and overall survival (median 11.8 months; 95% CI 7.6-15.2 months), solid line.

DISCUSSION

Although older and frail patients are underrepresented in clinical trials, palliative chemotherapy prolongs OS and enhances quality of life for all patients, including those who are older. In big randomised studies, the median OS is getting close to 12 months, but in unselected populations, it is substantially lower [17,18]. Although individuals in many current studies are highly chosen and the median age is frequently only about 60 years, patients with aEGA typically have a median age of approximately 70 years. There are numerous first-line regimens that have been approved for use in this situation, but no global combination has yet to receive a unanimous endorsement. The cornerstone of first-line therapy is a combination of a platinum-based chemotherapy (cisplatin or oxaliplatin) and a fluoropyrimidine (fluorouracil, capecitabine, or S-1) [2,3,9,19,20]. Even if it increases toxicity, the addition of docetaxel to such doublets improves OS even further. 455 patients from 72 centres and 16 countries were randomly assigned to receive triple DCF (docetaxal, cisplatin, and fluorouracil) or CF in the V325 study [8]. With a larger RR (37 percent Vs. 25 percent), longer PFS (5.6 Vs. 3.7 months), and a longer median OS, DCF was substantially more effective than CF alone (9.2 Vs. 8.6 months). The maintenance of quality of life and therapeutic benefit favoured DCF over CF [21,22] despite the fact that DCF resulted with an increased risk of serious adverse events, including febrile neutropenia and/or neutropenic infection (29 percent Vs. 12 percent) and diarrhoea (19 percent Vs. 8 percent). The effectiveness of taxanes has been supported by numerous more trials and meta-analyses [10,11,13,23,24], and the most effective schedule has not yet been determined. Currently, a triple taxane combination is the most promising one: Important questions regarding treatment every second or third week, oxaliplatin or cisplatin, fluorouracil infusion or oral substitutes, and docetaxel dosage remain unanswered [9,25].
According to recent updates, three-drug regimens significantly improve OS when compared to two-drug regimens, although at the expense of greater toxicity [9,26].

The current phase II investigation examines the combination of DOX in patients with aGEA based on our phase I dose discovery study [14]. With an RR of 66 percent, PFS of 7.7 months, and OS of 11.8 months, the effectiveness findings of the current study are consistent with those of other western phase II trials [23,24,27-29], whose reported median PFS ranged from 5.2 to 6.9 months and OS from 8.4 to 18 months. Due to the present study's unacceptably hazardous level of febrile neutropenia, a dose change was required. Only 6 of 30 patients (20%) experienced febrile neutropenia after the 15% dose reduction of docetaxel and oxaliplatin, compared to 8 of 12 patients (66%) who got high dose DOX. The effectiveness of the medication was unaffected by this dose adjustment. The triple regimen has a significant

haematological toxicity, hence some writers have adjusted it to include split or lowered doses of all three medications, with acceptable outcomes and controllable toxicity [26]. In specifically, Shah, et al. [11] conducted a phase II randomised research contrasting a modified DCF regimen with the usual docetaxel, cisplatin, and 5-FU (DCF) regimen. Granulocyte colony-stimulating factor (G-CSF) was used, although the conventional DCF arm was prematurely shut down because to high toxicity. G-CSF was not consistently made available to the patients in the current investigation. The most recent ESMO Clinical Practice guidelines [30] advise using G-CSF prophylactically if the probability of febrile neutropenia for all anticipated treatment cycles is greater than 20%. Some of the individuals in the current study might not develop febrile neutropenia if G-CSF was made available to them. As observed in the study by Shah, et al. [11], where the adjusted schedule provided treatment every second week, altering the treatment schedule in addition to administering G-CSF may also lessen the side-effects. In contrast to the adverse effects, the mix of the chemotherapy drugs is crucial. In a three-drug combination that also included docetaxel and oxaliplatin, a recent randomised phase II trial examined whether capecitabine could take the place of 5-FU [24]. Docetaxel plus oxaliplatin (DO), docetaxel, oxaliplatin, and 5-FU (DOF), or docetaxel, oxaliplatin, and capecitabine were given at random to the patients (DOX).

The identical dose of DOX as in the current study was administered. Patients receiving treatment every two weeks had stronger efficacy and a lower incidence of febrile neutropenia, according to the author. It needs to be determined whether this is due to the combination of 5-FU and a slightly reduced dose of docetaxel given every two weeks. Capecitabine or S-1 is frequently given for 14 days every three weeks when oral therapy is used to replace 5-FU infusions, but a two-week programme of docetaxel, oxaliplatin, and S-1 is tolerated and encouraging [25]. A median OS of more than 12 months has never been demonstrated in a major Western randomised study (more than 100 patients per treatment arm), and it is not anticipated that this will change significantly with the existing marketed and licenced cytotoxic medicines. There has been a lot of interest in combining biological agents with the greatest chemotherapy regimens, which has been sparked in part by the findings of previous approaches. In patients with HER2 overexpression, the most promising treatment option is currently found. Since it is well tolerated, trastuzumab can be used in triple docetaxel regimens with extremely encouraging outcomes [31]. In conclusion, individuals with advanced gastro-esophageal cancer can receive DOX (D 51 mg/m2 day 1, O 100 mg/m2 day 1, and X 1250 mg/m2) continuously every three weeks. The efficacy of this treatment is highly encouraging and merits further study in larger studies.

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CONFLICT OF INTERESTS

Author declares no conflict of interest. The author alone is responsible for the content and writing of the paper.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin Nov 68: 394-424.

2. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, et al. (2010) Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 8: CD004064.

3. Lordick F, Lorenzen S, Yamada Y, Ilson D (2014) Optimal chemotherapy for advanced gastric cancer: Is there a global consensus? Gastric Cancer 17: 213-225.

4. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, et al. (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358: 36-46.

5. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, et al. (2009) Capecitabine/cisplatin versus 5 fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: A randomised phase III noninferiority trial. Ann Oncol 20: 666-673.

6. Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, et al. (2008) 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 26: 1435-1442.

7. Schonnemann KR, Jensen HA, Yilmaz M, Jensen BY, Larsen O, et al. (2008) Phase II study of short-time oxaliplatin, capecitabine and epirubicin (EXE) as first-line therapy in patients with non-resectable gastric cancer. Br J Cancer 99: 858-861.

8. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, et al. (2006) 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: 4991-4997.

9. Ter Veer E, Haj Mohammad N, van Valkenhoef G, Ngai LL, Mali RM, et al. (2016) The Efficacy and Safety of First-line Chemotherapy in Advanced Esophagogastric Cancer: A Network Meta-analysis. J Natl Cancer Inst 108.

10. Wang J, Xu R, Li J, Bai Y, Liu T, 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: 234-244.

11. Shah MA, Janjigian YY, Stoller R, Shibata S, Kemeny M, et al. (2015) Randomized Multicenter Phase II Study of Modified Docetaxel, Cisplatin, and Fluorouracil (DCF) Versus DCF Plus Growth Factor Support in Patients With Metastatic Gastric Adenocarcinoma: A Study of the US Gastric Cancer Consortium. J Clin Oncol 33: 3874-3879.

12. Van Cutsem E, Lenz HJ, Kohne CH, Heinemann V, Tejpar S, et al. (2015) Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J Clin Oncol 33: 692-700.

13. Wagner AD MM, Grothe W, Haerting J, Unverzagt S (2015) Novel chemotherapy combinations for metastatic gastric adenocarcinoma (mAGC): An updated meta-analysis. J Clin Oncol 33.

14. Andersen M, Schonnemann KR, Yilmaz M, Jensen HA, Vestermark LW, et al. (2010) Phase I study of docetaxel, oxaliplatin and capecitabine (TEX) as first line therapy to patients with advanced gastro-oesophageal cancer. Acta Oncol 49: 1246-1252.

15. Schonnemann KR, Yilmaz M, Andersen M, Pfeiffer P (2011) New recommendation of doses in an ongoing phase II study of docetaxel, oxaliplatin and capecitabine as first line therapy in advanced gastro-oesophageal cancer. Acta Oncol 50: 151-152.

16. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10: 1-10.

17. Schonnemann KR, Mortensen MB, Bjerregaard JK, Fristrup C, Pfeiffer P (2014) Characteristics, therapy and outcome in an unselected and prospectively registered cohort of patients with gastro-oesophageal cancer. Acta Oncol 53: 385-391.

18. Yang D, Hendifar A, Lenz C, Togawa K, Lenz F, et al. (2011) Survival of metastatic gastric cancer: Significance of age, sex and race/ethnicity. J Gastrointest Oncol 2: 77-84.

19. Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, et al. (2014) Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Radiother Oncol 110: 189-194.

20. Ajani JA, Bentrem DJ, Besh S, D'Amico TA, Das P, Denlinger C, et al. (2013) Gastric cancer, version 2.2013: Featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 11: 531-546.

21. Ajani JA, Correa AM, Swisher SG, Wu TT (2007) For localized gastroesophageal cancer, you give chemoradiation before surgery, but then what happens? J Clin Oncol 25: 4315-4316.

22. Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, et al. (2007) Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: The V-325 Study Group. J Clin Oncol 25: 3210-3216.

23. Al-Batran SE, Pauligk C, Homann N, Hartmann JT, Moehler M, et al. (2013) 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 49: 835-842.

24. Van Cutsem E, Boni C, Tabernero J, Massuti B, Middleton G, et al. (2015) Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: A randomized phase II study. Ann Oncol 26: 149-156.

25. Pfeiffer P, Qvortrup C, Krogh M, Schoennemann K, Vestermark LW, et al. (2017) S-1 in combination with docetaxel and oxaliplatin in patients with advanced gastro-esophageal adenocarcinoma: Two parallel phase 1/2a studies. Acta Oncol 56: 46-51.

26. Petrelli F, Tomasello G, Ghidini M, Passalacqua R, Barni S (2017) Modified schedules of DCF chemotherapy for advanced gastric cancer: a systematic review of efficacy and toxicity. Anticancer Drugs 28: 133-141.

27. Amarantidis K, Xenidis N, Chelis L, Chamalidou E, Dimopoulos P, et al. (2011) Docetaxel plus oxaliplatin in combination with capecitabine as first-line treatment for advanced gastric cancer. Oncology 80: 359-365.

28. Goel G, Jauhri M, Negi A, Aggarwal S (2010) Feasibility study of docetaxel, oxaliplatin and capecitabine combination regimen in advanced gastric or gastroesophageal adenocarcinoma. Hematol Oncol Stem Cell Ther 3: 55-59.

29. Stein A, Arnold D, Thuss-Patience PC, Moehler M, Grothe W, et al. (2014) Docetaxel, oxaliplatin and capecitabine (TEX regimen) in patients with metastatic gastric or gastro-esophageal cancer: Results of a multicenter phase I/II study. Acta Oncol 53: 392-398.

30. Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, et al. (2016) Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol 27: v111-v118.

31. Al-Batran SE, Hozaeel W, Jager E (2012) Combination of trastuzumab and triple FLOT chemotherapy (5-fluorouracil/leucovorin, oxaliplatin, and docetaxel) in patients with HER2-positive metastatic gastric cancer: Report of 3 cases. Onkologie 35: 505-508.

