Original Article

Phase I/II trial of triplet regimen with docetaxel, oxaliplatin and capecitabine in advanced gastric and gastroesophageal cancers

Prasad Eswaran, Kalaichelvi Kannan, Srinivasan Lakshmi Narasimhan, Balaji, Suresh Kumar, Durai Mavalavan

Department of Medical Oncology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India

ABSTRACT

Background: Advanced and metastatic gastric cancers present at late stages and have very dismal prognosis. Many modifications have been tried for improving the outcome. Docetaxel, cisplatin and fluorouracil/epirubicin, cisplatin and fluorouracil regimen have been established as a standard combination in clinical trials; however, they are limited by their toxicities. **Aim:** We conducted a study to assess the maximal tolerated dose (MTD) of docetaxel given at days 1 and 8 along with fixed doses of oxaliplatin (days 1 and 8) and capecitabine (days 1–14), toxicity profile, response rate and efficacy of the triplet combination in advanced/metastatic gastric and GEJ malignancies. **Materials and Methods:** Study was conducted in two phases; Phase I study assessed the MTD and Phase II assessed toxicity, response and efficacy of polychemotherapy. Escalating doses of docetaxel was tested in Phase I design along with oxaliplatin 50 mg/m^2 (days 1 and 8) and capecitabine 625 mg/m^2 (days 1–14). MTD dose of docetaxel was used in Phase II along with the other two drugs for assessment of primary and secondary endpoints. **Results:** A total of 24 patients were evaluated in Phase I design as per modified Fibonacci series. The MTD for docetaxel was 40 mg/m^2 given on days 1 and 8. On evaluation of 27 patients in Phase II, hematological, neurological and biochemical toxicities were tolerable. Grade 3 diarrhea and hand-foot syndrome were the most common toxicities. Overall response rates were 66.6%. Median progression-free survival (PFS) was 8.4 months. **Conclusion:** The MTD of docetaxel was 40 mg/m^2 (days 1 and 8) administered along with oxaliplatin 50 mg/m^2 (days 1 and 8) and capecitabine 625 mg/m^2 (days 1–14). The regimen had proven to be efficacious with appreciable overall response rates, PFS with tolerable and manageable toxicities.

Key words: Capecitabine, docetaxel, gastric cancer, oxaliplatin

INTRODUCTION

Advanced gastric cancer includes locally advanced inoperable disease and metastatic disease. While one-third of the cases present at unresectable state, another one-third as metastatic disease (M1). It also includes relapsing disease that was initially operated and constitutes about 60% of all cases. Thus, overall 80–90% of the cases will have advanced disease.[1] Advanced gastric cancer represents a challenging problem across the world with poor response to systemic chemotherapy. Most cancers diagnosed at very advanced stages are often unresectable. Even after a curative resection, the relapse rates in many studies are high without chemotherapy (40–60%) and the median survival is estimated to be 3–5 months.[2] There are few improvements in the efficacy of treatments as the median survival is between 9 and 12 months. Of the various regimens, epirubicin, cisplatin and fluorouracil (ECF)/ECX/EOX (REAL 2 study), docetaxel, cisplatin and fluorouracil (DCF) (V325 trial) and

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Address for correspondence: Dr. Prasad Eswaran, Department of Medical Oncology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai - 600 003, Tamil Nadu, India. E-mail: drprasadsen@hotmail.com

FOLFIRI are considered as optimal first-line chemotherapy regimen in advanced cases for clinical trials. Doublets with cisplatin, oxaliplatin, fluoropyrimidines and irinotecan are considered acceptable options based on noninferiority trials.[3] Most patients attending to hospitals in this part of the country are in the fourth and fifth decade of life with advanced disease and moderate to poor performance status. Secondary to poor nutrition attributed to disease status. We tried to assess the maximal tolerated dose (MTD), toxicity, response rates and efficacy of tripet regimen with modified regimen of docetaxel (D), oxaliplatin (O) and capecitabine (X) in advanced gastric and GEJ tumors.

MATERIALS AND METHODS

Patient selection

Patients aged 18–65 years with histological proof of diagnosis of gastric/gastroesophageal junction malignancies, Eastern Cooperative Oncology Group (ECOG) ≤2, with adequate hematological (neutrophil count >1500 cells/mm^3, platelets >100,000 cells/mm^3), hepatic (serum bilirubin <1.5 × upper limit of normal [ULN], transaminase <3 × ULN) and renal parameters (calculated renal clearance >50 ml/min) were included in the study. Patients who were chemotherapy naïve and with prior exposure of one or two lines of treatment were also included [Table 1]. Other inclusion criteria were ability to tolerate oral medication, no peripheral neuropathy, no co-existent severe medical illnesses, no sign of brain metastases and no concomitant treatment with other antineoplastic agents. Pregnant or lactating females were excluded. The study was approved by Institutional Review Board, and all patients were required to sign informed consent prior to enrollment.

Table 1: Patient characteristics

Patients enrolled	52
Median age, years	52 (27-69)
Male:Female	38 (73%):14(27%)
ECOG 1	6 (11.5%)
ECOG 2	43 (82.7%)
ECOG 3	3 (5.8%)
III A	14 (26.9%)
III B	11 (21.2%)
III C	12 (23.1%)
IV	15 (28.8%)
Site of metastases	
Liver	7
Lymph nodes	41
Peritoneum	3
Liver+peritoneum	3
Left supraclavicular adenopathy	4
Lung	1
Prior therapy	
Surgery	35 (67.3%)
Palliative gastrectomy	9
Gastrojejunostomy	23
Feeding jejunostomy	3
Chemotherapy-1st line exposed	13 (25%)
Chemotherapy naïve	39 (75%)
Lost for follow up	6
Not beyond 4 cycles	5

All eligible patients were evaluated with upper gastrointestinal endoscopy and histology documented by biopsy of the lesion. Surgical feasibility was assessed with computed tomography (CT) scan of the abdomen and pelvis and laparoscopic evaluation prior to definitive surgery. Operable cases underwent surgical evaluation. Intraoperative findings were noted for documenting intra-abdominal disease for metastatic status. Patients with clinicoradiological evidence of metastases were started on palliative chemotherapy after cytological confirmation of the disease at metastatic site/primary site.

Chemotherapy regimen

Premedication with dexamethasone 8 mg PO was taken 3 times, the previous night, the morning of and the evening after docetaxel administration for reducing the incidence of fluid retention. Doses of oxaliplatin and capecitabine were fixed at 50 mg/m^2 (days 1 and 8) and 625 mg/m^2 (days 1–14) respectively. Docetaxel was started at 25 mg/m^2 (days 1 and 8) and escalated with 5 mg/m^2 at each dose level. Therapy was continued until the dose-limiting toxicity is reached. Docetaxel and oxaliplatin were administered as 1 h infusion in normal saline and 5% dextrose solution respectively. Capecitabine was advised to be taken orally with water within 30 min of food ingestion as twice daily dosage for 14 days. All patients were advised to avoid friction causing activities and excessive manual work to prevent hand-foot syndrome (HFS). Supplement with pyridoxine tablets 100 mg/day were prescribed during treatment. Compliance for oral medications was checked by tablet counts at each clinical visit. The cycle was repeated every 21 days for a maximum of six cycles unless stopped due to progressive disease, toxicity or patient's refusal.

Phase II study was designed to include patients at MTD dose of docetaxel, 50 mg/m^2 of oxaliplatin and 625 mg/m^2 of capecitabine in all cases recruited for two stages of the study. Modifications and delays were planned based on the toxicity. Administration of the drugs was delayed until hematological recovery (TC >3000 cells/mm^3, ANC >1500 cells/mm^3 and platelet >10,000 cells/mm^3) is adequate. If an episode of grade 4 hematological serious adverse event (SAE) occurred, dose of deocetaxel was reduced by 25%. A second SAE would warrant a reduction to 50% dose. Capecitabine was interrupted immediately on the development of grade >2 diarrhea, stomatitis or HFS and resumed after the toxicity had recovered to grade <1. Daily dose of capecitabine was reduced to 25% at incidence of grade 3 toxicity or second incidence of grade 2 toxicity, 50% at second incidence of grade 3 toxicity or first incidence of grade 4 nonhematological toxicity. Doses of docetaxel and oxaliplatin were reduced to 25% in case of ≥grade 3 neuropathy. Second incidence would necessitate dose reduction to 50%.

Toxicity assessment during treatment and follow-up

Dose-limiting toxicities (DLT) were defined as grade 3/4 hematological toxicity (persisting more than 7 days), persistent neuropathy (>14 days) or nonhematologic toxicity (persisting more than 7 days) during the course of therapy. A minimum of three patients were included in each cohort. If no excessive toxicity was observed in each cycle, dose of docetaxel is escalated by 5 mg/m^2. If DLT was observed in one patient, then the dose level was expanded to include three more patients. Dose escalation continued if DLT occurred in 2 out of 6 patients. If three or more instances of DLT occurred among six patients, the preceeding dose level was defined as the MTD. Toxicities were graded as per NCI Common Toxicity Criteria for Adverse Events (CTCAE version 4.0). Treatment was usually withheld for 1 week until toxicity returns to grade 1 or less. Persistent toxicity was also considered as DLT. The trial was planned for Phase II after MTD was confirmed in another cohort of patients on MTD. Anemia was not included as SAE as the cause may be multifactorial in gastric cancer.

All patients were evaluated with blood counts, liver function, and renal function tests prior to each admission on days 1 and 8. CT scan of the abdomen and pelvis was done at the end of three cycles and six cycles to monitor disease status and response during treatment. Patients were evaluated with blood investigations and CT scans at 3 monthly intervals thereafter.

Study methodology

Phase I

The primary endpoint of Phase I design was to assess the MTD. Study methodology used in this design was modified Fibonacci sequence. Cohorts of 3–6 patients were included in each level. All eligible cohorts in each level had oxaliplatin started at 50 mg/m^2 and capecitabine 625 mg/m^2 given at fixed doses on days 1–8 and days 1–14 respectively. The dose of docetaxel was started at 25 mg/m^2 and was escalated at 5 mg/m^2 per level if there are no DLT at that level. If the incidence of DLT is 33% in a group, then three additional patients were treated at the same level. If no further case with DLT was observed in the additional cohort, dose escalation was continued. If the incidence of DLT was >33% at any level, dose escalation was stopped. The Phase II recommended dose was the highest dose for which the incidence of DLT is < 33%. Usually, six or more patients were treated at the recommended level to confirm the MTD before proceeding to Phase II.

Phase II

The primary endpoint of Phase II design was to assess the efficacy of this combination in terms of objective overall response rates (ORRs). Secondary endpoints in this phase were progression-free survival (PFS) and overall survival (OS). Patients were analyzed if they completed four cycles of chemotherapy. Otherwise, they were included as nonresponders in analysis. Methodology employed in Phase II study was Simon's two-stage optimal design, assuming that the ORR would be of 40%, and the minimum acceptable response of 18% is achieved. This would include a sample size of 13 patients in first stage. If a minimum of three responses were observed, additional 14 patients were included in the second stage of the disease. The treatment regimen was considered efficacious if eight responses were observed of 27 evaluable cases. The probability of accepting a treatment with a real response rate of <17% would be 5%. However, the risk of rejecting a treatment with a response rate of >40% would be 10%.

RESULTS

Results of Phase I study

Totally, 24 newly diagnosed patients were enrolled for Phase I, three patients in dose level 1 (25 mg/m^2) and 2 (30 mg/m^2), six patients in dose level 3 (35 mg/m^2) and 4 (40 mg/m^2) and three patients in level 5 (45 mg/m^2). Three patients were included at MTD level (40 mg/m^2). Table 2 depicts the details of Phase I study.

Level 1

Three patients recruited on dose level 1 received all of the prescribed six chemotherapy cycles without any dose reductions or DLT. There was an episode of self-limiting incidence of melena, but treatment was not hindered. Supportive therapy with blood transfusion was given for correction of anemia. Two patients had grade 2 diarrhea.

Level 2

Three patients recruited on dose level 2 completed six cycles of chemotherapy without any DLT. One patient discontinued treatment after three cycles and was excluded from the cohort. One patient had grade 3 diarrhea but settled within 7 days, hence not considered as SAE. Another patient had grade 2 diarrhea.

Table 2: Dose levels and Serious Adverse Events (SAE) in phase I study

Level	No. of pts	Dose of docetaxel (mg/m^2)	Dose of oxaliplatin / capecitabine (mg/m^2)	Dose Limiting Toxicity (DLT)
1	3	25	50/625	None
2	3	30	50/625	None
3	6 (3+3)	35	50/625	1 HFS
4	9 (3+3+3)	40	50/625	1 HFS 1 Febrile neutropenia
5	3	45	50/625	2 Febrile neutropenia

Level 3

Three patients were recruited at level 3, of which one patient developed grade 3 HFS and subsequently improved with salicylic acid cream. As it was a SAE [Figure 1], an additional cohort with three patients were included and continued on the same dose level. No additional SAE was encountered in this group. One patient needed blood transfusion for anemia. Grade 2 diarrhea was present in all patients.

Level 4

Three patients were started on level 4. There was an episode of febrile (grade 3) neutropenia designated as SAE. Three more patients included in the same dose level did not experience any SAE. One patient needed blood transfusion for correction of anemia. Grade 2 diarrhea was present in two patients. One patient had delayed 4th cycle by 2 weeks but completed all cycles of chemotherapy.

Level 5

Three patients were enrolled on level 5. Two episodes of febrile (grade 3) neutropenia were encountered, after 3rd cycle and 6th cycle of chemotherapy necessitating use of granulocyte stimulating factor support. These events were designated as SAE and were defined as DLT. Patient who developed grade 3 neutropenia after 3rd cycle of chemotherapy was lost for further follow-up. Further accrual was stopped as DLT was reached, and the previous level was considered as MTD as per the predefined toxicity criteria.

Maximal tolerated dose level

Three additional patients were included at this dose level. All completed six cycles of chemotherapy. There was one episode of grade 3 HFS seen in one patient. There were two episodes of grade 2 and one episode of grade 3 neutropenia that improved with supportive care within 7 days and were not considered as SAE.

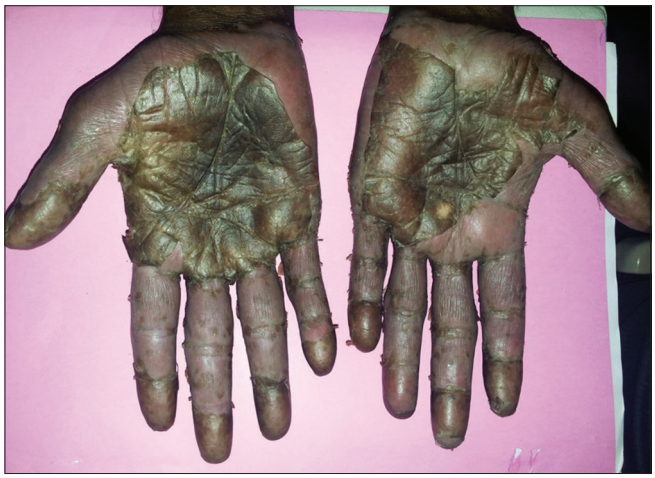

Figure 1: Grade 3 hand-foot syndrome – Severe skin changes with pain limiting self-care activities of daily living

There were nine patients included in dose level 4. There was an episode of grade 3 neutropenia in the first cohort. The second cohort had no SAE. The third cohort had one episode of grade 3 HFS. There were 2 SAE in nine patients that was <33% as defined by modified Fibonacci series. Based on the SAE experienced in previous cohorts, level 4 (docetaxel dose 40 mg/m^2) was considered as MTD.

Results of Phase II study

Totally, 18 new patients were recruited for Phase II study design. Nine patients treated at MTD in Phase I were included in Phase II study. Four new patients were recruited in the first stage of the study and response was evaluated. Since the response was significant in 13 cases included in the first stage, trial was continued to second stage that included 14 cases, thereby evaluating required sample size for meaningful results.

Toxicity

A total of 27 patients were evaluable for toxicity assessment [Table 3]. Grade 2 neutropenia was present in 18 (66%) patients. Grade 3 neutropenia was minimal and present in 2 (7.6%) patients. Four (14.8%) patients had grade 2 anemia. Grade 3 and grade 2 diarrhea were present in 4 (14.8%) patients and 15 (55.5%) patients respectively.

Hand-foot syndrome was the most common nonhematological complication seen in the study population. Grade 2 HFS was present in 6 (22.2%) patients. One patient had grade 3 HFS after 4th cycle, and subsequent doses were reduced to 50%. Two patients with grade 2 toxicity were managed with dose delays and completed all courses of chemotherapy. All patients developed complications after 4th cycle of chemotherapy.

Table 3: Toxicity profile in phase II study. (for 27 cases analyzed for phase II study)

	Grade 1	Grade 2	Grade 3	Grade 4
Total leucocyte count	1 (3.7)	21 (77.7)	5 (18.5)	-
Thrombocyto penia	9 (33.3)	2 (7.4)	-	-
Anemia	13 (48.1)	4 (14.8)	-	-
Neutropenia	7 (25.9)	18 (66.6)	2 (7.4)	
Vomiting	8 (29.6)	-	-	-
Diarrhea	8 (29.6)	15 (55.5)	4 (14.8)	-
Abdominal distension	7 (25.9)	2 (7.4)	-	-
Abdominal pain	2 (7.4)	1 (3.7)	-	-
Ascites	4 (14.8)	-	-	-
Hand foot syndrome	13 (48.1)	6 (22.2)	1 (3.7)	-
Paronychia	5 (18.5)	2 (7.4)	-	-
Neuro (motor)	1 (3.7)	4 (14.8)	-	-
Neuro (sensory)	6 (22.2)	15 (55.5)	-	-
Fatigue	5 (18.5)	20 (74)	-	-
Anorexia	10 (37)	12 (44.4)	1 (3.7)	-
Alopecia	3 (11.1)	24 (88.8)	-	-
Total bilirubin	2 (7.4)	-	-	-
SGOT	2 (7.4)	8 (29.6)	-	-
SGPT	3 (11.1)	7 (25.9)	-	-
Alkaline phosphatase	1 (3.7)	-	-	-
Creatinine	1 (3.7)	-	-	-

**Parentheses contains percentages (%)

Paronychia was observed in 2 (7.4%) patients with grade 2 toxicity and was managed symptomatically with oral antibiotics and analgesics. Five (18.5%) patients had grade 1 toxicity.

Total alopecia (grade 2) was seen in 24 (88.8%) of patients. Patchy (grade 1) hair loss was seen in 3 (11.1%) cases only.

The most disabling adverse event in the study group was loss of sensory functions due to oxaliplatin induced neuropathy. Grade 2 sensory neuropathy was present in 15 (55.5%) cases and was the most common symptom after 5th cycle. The intensity slowly regressed over a period of 4–6 months after completion of treatment in a majority of the cases; however, the symptoms were more subjective and variable during follow-up. Definitive grading of motor deficit could not be made out due to associated pain component. However, it was relatively less when compared to sensory deficits.

Changes in performance status

The majority (43 of 52–82.6%) of the cases belonged to ECOG 2 at enrollment. Three cases (5.7%) with ECOG 3 were recruited due to young age with advanced disease status. There was no decline in performance status, and most patients were able to get appreciable symptom relief that reflected in the improvement of their performance status during therapy. Assessment of performance status revealed significant improvement in ECOG score in the initial cohort of patients participated in Phase I study. Change in general condition due to improvement in disease-related symptoms was noted after 3rd chemotherapy cycle in many patients in Phase II study. However, there was a subjective increase in fatigue during later cycles of chemotherapy (74%) corresponding to decline in ECOG score.

Response rates/efficacy/survival

At the completion of the study, 52 patients were treated in both Phases I and II studies. One patient discontinued treatment in Phase I. Three patients did not complete beyond three cycles in Phase II study. Six patients were lost for follow-up after completion of therapy and were not included in the assessment of survival data. However, they were included in response assessment making a total of 33 patients evaluable for analysis. The majority of the cases included inoperable, advanced and metastatic disease. Partial response (PR) was appreciated in 18 (54.5%) and complete response (CR) in 4 (12.1%) cases. Stable disease was present in 3 (9.1%) cases. There was progressive disease in 8 (24.3%) cases. Disease control rate with this regimen in this study was 75.7%.

Complete responses were seen in four cases (one in liver who underwent prior gastrectomy and metachronously developed liver metastases, second with inoperable primary due to cirrhotic liver, third who underwent gastrectomy and residual lymph nodes were left behind following an inadequate dissection and had positive surgical margins and fourth with inoperable disease with pancreatic infiltration).

Median PFS was 8.4 months (90% confidence interval 7.4–9.4 months). OS was not reached in the study population. Of the 27 cases, four patients were alive at the time of this writing. Eight patients developed progressive ascites and liver metastases and were started on second line chemotherapy with a doublet regimen. Four patients developed obstructive jaundice and were treated with best supportive care. Six cases had poor general condition at the time of progression and were treated with weekly 5 FU bolus regimen. Five patients were lost for further management after the diagnosis of disease progression.

DISCUSSION

Advanced gastric/gastroesophageal tumors remain a challenge to the treating physician with relatively poor survival rates. Chemotherapy had been the mainstay of treatment backbone to improve the survival and quality of life. In Europe, the preferred regimen is ECF and considered the standard of care. ECF is associated with practical difficulties of prolonged drug infusion, need for intravenous access devices and use of anthracycline is associated with late cardiotoxicity. REAL 2 trial had proven equivalence of cisplatin and 5 FU with oxaliplatin and capecitabine respectively, and authors have suggested using them interchangeably.[4] EOX regimen had significantly less neutropenic episodes and nephrotoxicity when compared with ECF but more incidences of diarrhea and peripheral neuropathy. Recent trials had evaluated the use of oxaliplatin with fluoropyrimidine analogs with appreciable results without much toxicity as associated with cisplatin. Response rates are in the order of 30–60% with much reduced neutropenic episodes and nephrotoxicity making it an excellent drug option for combination chemotherapy in first and second line management of gastric cancers.

Capecitabine has been recommended for gastric cancers replacing 5 FU based on clinical activity and response rates up to 40%. Conventional doses were modified to improve tolerability. Higher doses of capecitabine were given for shorter periods by Scheithauer *et al*.[5] who demonstrated improved PFS with 7-day regimen repeated every 14 days compared with 14 days regimen every 21 days. A reduced dose of capecitabine in 10 days course had been used by Evans *et al*.,[6] with the cycle repeated every 21 days. Di Lauro *et al*.[7] and Amarantidis *et al*.[8] used a continuous 21 days regimen but with lower (500 mg/m^2

BD) and higher (1250 mg/m^2 BD) respectively in advanced stages of gastric cancer. We tried an intermediate dose of 625 mg/m^2 BD for 14 days in this study as it is combined with other active drugs.

Presently, there is no specific recommendation for any specific regimen. However, National Comprehensive Cancer Network guidelines on gastric cancer (Version 2.2013) recommend 2 drug regimen due to lower toxicity. However, the consensus is to give triplet regimen (DCF) for medically fit and patients with good performance status. DCF regimen is associated with high incidence of toxicities when compared to cisplatin-containing doublet regimen. Few studies reported the superiority of docetaxel based regimen over another regimen. Roth *et al*.[9] had demonstrated a superior benefit using DCF over ECF and DC regimen with better response rates (36.6% vs. 25% vs. 18.5%) and higher toxicity (neutropenia - 57% vs. 34% vs. 49%). Another similar study comparing the three combinations was reported by Kilickap *et al*. with comparable results.[10] The major complication associated with DCF regimen was neutropenia. A meta-analysis of 12 randomized controlled trials by Chen *et al*. demonstrated the superiority of docetaxel containing regimen compared to nontaxane containing palliative chemotherapy.[11]

Newer modifications and substitutions were employed to reduce the toxicity of DCF regimen. Substitution of oxaliplatin reduces nausea, vomiting and nephrotoxicity and capecitabine replace the need for prolonged infusion used in V325 trial by Van Cutsem *et al*.[12] Docetaxel dose ranged from 60 to 75 mg/m^2 given every 21 days in combination with oxaliplatin and capecitabine. Docetaxel was planned at weekly doses to reduce the major adverse event of neutropenia. Many trials had evaluated lower doses of the drug given at weekly schedules to lower the hematologic toxicity. MTD of docetaxel had a range of 25–30 mg/m^2 given on days 1 and 8. We achieved a MTD of 40 mg/m^2 (days 1 and 8) along with oxaliplatin 50 mg/m^2 (days 1 and 8) and capecitabine 625 mg/m^2 (days 1–14) in this study. Diarrhea, HFS, and febrile neutropenia were the most common DLT in various trials. We have experienced HFS and neutropenia as DLT in this trial consistent with the reported data in literature.

Phase II design was conducted with the MTD and achieved results comparable with the available evidence. Response rates ranged from 29% to 79% with various schedules of the triplet combination regimen. ORR achieved in this study was 75.7% with CR of 12.1% and PR 54.5%. Stein *et al*.[13] had reported a Phase I/II study with 43% ORR with 4% CR and 39% PR [Table 4]. Amarantidis *et al*. reported a better ORR of 59% with this regimen with a CR of 15% and PR of 44%. In V325 trial with DCF regimen, ORR of 37% (CR - 2%/ PR - 35%) was reported. REAL 2 study reported ORR of 47.9%, 40.7%, 42.2% and 46.4% with EOX, ECF, EOF and ECX respectively.

Table 4: Response rates according to RECIST v1.1 criteria

(Total sample size completed >4 cycles=33 cases)	No. of cases	Percentage
Complete response	4	12.1
Partial response	18	54.5
Stable disease	3	9.1
Progressive disease	8	24.3

Hematologic toxicity was the main concern of docetaxel containing regimen. V325 trial had a high neutropenia incidence of 82% compared to cisplatin-based regimen (57%). Substituting cisplatin with oxaliplatin had reduced the incidence of severe neutropenia by decreasing overlapping myelosuppressive properties of chemotherapeutic drugs. We have encountered a DLT of grade 3 febrile neutropenia at MTD. However, the neutropenic episode was manageable. In the Phase II study, the incidences of grade 3 neutropenia were minimal (7.4%). The majority of the cases had grade 2 neutropenia (66.6%) and there was no requirement of granulocyte colony stimulating factors in the study. As with the study by Amarantidis *et al*., it was demonstrated with 6% incidence of febrile neutropenia. Stein *et al*. reported a low incidence of 9% grade 3/4 neutropenia.

Diarrhea and HFS are the most common nonhematological toxicity associated with the use of capecitabine. We had 14.8% incidence of grade 3 and 55.5% incidence of grade 2 diarrhea, comparable to the data reported in the literature. This had been a main reason for treatment discontinuation in few studies and was the DLT in Phase I clinical trials. Another Phase II study had reported a higher incidence (30%) grade 3 diarrhea. There were variable incidences of diarrhea with another regimen (FLOT 14.8%, DCF 19%, DCX 11.8%) varying in a range between 7% and 24%. Careful monitoring with early dose delays and interruptions were more efficient in managing mucosal toxicities.

Hand-foot syndrome is one of the SAE reported in our trial. The incidence of grade 3 was reported in one (3.7%) patient. Grade 2 toxicity was reported in 6 (22.2%) cases. Trials that had reported HFS as a serious adverse event had either used a higher dose or continuous use of the drug. A study[14] reported the incidence of HFS in combination chemotherapy as high as 20% in clinical trials. Grade 3 HFS were reported in 2.4% to 6.3% of patients receiving capecitabine containing (ECX, DCX, EOX or CX) regimen.

The overall hematological and nonhematological toxicity profile of this regimen was manageable and tolerable. Due to comparable efficacy, better tolerability and feasibility

of the regimen, the triplet combination of docetaxel with oxaliplatin and capecitabine had been shown to have promising activity in advanced gastric and gastroesophageal cancer.

CONCLUSION

The MTD of docetaxel is 40 mg/m^2 (days 1 and 8) administered along with oxaliplatin 50 mg/m^2 (days 1 and 8) and capecitabine 625 mg/m^2 (days 1–14) and was recommended for Phase II study. Grade 3 HFS and neutropenia were the DLT in the Phase I study. The regimen had proven to be efficacious with appreciable ORRs, progression and OS with tolerable and manageable toxicities in Phase II study. The regimen needs further validation in randomized controlled Phase III design in advanced stages of gastric cancers.

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Conflict of interest
There are no conflict of interest.

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