Docetaxel, Cisplatin and Fluorouracil (DCF) versus Epirubicine, Cisplatin & Fluorouracil (ECF) as a first-line therapy in advanced gastric carcinoma patients

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Abstract

Background and Objectives: gastric carcinoma is still associated with a high mortality rates. Chemotherapy remains the primary treatment of this disease in advanced stage. This study was conducted to know the difference between docetaxel and epirubicin in combination with cisplatin and 5-flurouracil in Arabic patients with advanced gastric carcinoma.

Patients and Methods: Between February 2005 and December 2008 in multicentral phase III trial forty three eligible patients with advanced gastric carcinoma were randomly allocated to receive either Docetaxel 75mg/m^2 D1, Cisplatin 75mg/m^2 D1 and 5FU 1000mg/m^2 (over 6hrs) D1-3 in one arm {group A} or Epirubicine 50mg/m^2 D1 Cisplatin 75mg/m^2 D1 and 5FU 1000mg/m^2 (over 6hrs) D1-3 in the other arm as reference regimen {group B} Follow up of the surviving patients continued till the end of December 2009.

Aim of the study: The primary end point was progression free survival (PFS) while the secondary end points were response rate, overall survival (OS) and toxicity profile.

Results: Median PFS was found to be 6 months for group A (DCF) and 4.5 months for group B (ECF) and this difference was statistically significant with a P value of 0.035 and hazard ratio of 0.56 (95% CI ratio 0.234 to 0.949) and the overall response rate in group A was 36% (8 of 22 pts.) while that in group B was 29% (6 of 21 pts.). The median follow up period was 15.7 months, and the median OS for group A was 8.9 months while that for group B was 8.5 months but the differences in both OS and survival at one year were not statistically significant. Regarding the toxicities, both hematological and non hematological, were comparable in both groups except for neuropathy and diarrhea that were more pronounced in group A.

Conclusion: Both regimens were tolerable with acceptable toxicities with the DCF has a significant longer PFS than ECF but without significant difference in the OS.

Introduction

Gastric carcinoma has a relative low incidence, but remains a major cause of cancer related death worldwide and associated with high mortality figures due to the late stage at presentation in many cases as well as high relapse rates[(1)]. Clearly, gastric carcinoma is a complex disease with many clinical, pathological, and molecular features. Some new treatment strategies have been evolved in the last few years due to the expanding list of potential molecular markers for gastric carcinoma that provides an opportunity for better understanding the biology of he disease and then to develop new treatment options[(2)]. Combination chemotherapy regimens are still the main effective treatment for most of the advanced and metastatic cases of the disease with doubled survival ship when compared to best supportive care. Currently, there is no standard combination chemotherapy, although regimens include cisplatin and 5-fluorouracil (5FU) in addition to a third agent as epirubicine (ECF) or docetaxel (DCF) are widely used now and under many clinical trials. Also many other chemotherapeutic agents as oxaloplatin, capecitabine, or irinotecane are used in many other combinations[(3,4)]. So, we conducted this study to know the difference between docetaxel and epirubicine in combination with cisplatin and 5-flurouracil, in Arabic patients with advanced stage gastric carcinoma.

Patients and Methods

Between February 2005 and December 2008 forty three eligible patients with locally recurrent disease, advanced irresectable or metastatic gastric carcinoma were randomly allocated to receive either Docetaxel 75mg/m^2 D1, Cisplatin 75mg/m^2 D1 and 5FU 100mg/m^2 (over 6hrs) D1-3 in one arm {group A} or Epirubicine 50mg/m^2 D1 Cisplatin 75mg/m^2 D1 and 5FU 1000mg/m^2 (over 6hrs) D1-3 in the other arm {group B}. All patients should receive appropriate hydration and premedication. Treatment was continued till disease progression, unacceptable toxicity or patient's refusal. Follow up of the surviving patients continued till the end of December 2009.

Eligibility criteria included

Histolothgically confirmed locally advanced recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma, age: between 18-65years, performance status: ≤2 by ECOG, No prior chemotherapy and adequate haematologic, hepatic, renal and cardiac reserve:

Absolute neutrophil ≥1500/ml, platelets count ≥100,000/ml, Hgb ≥9gm/l, total bilirubin ≤1.5 ULN, transaminases ≤ 2.5 ULN, s. creatinine clearance ≥70ml/min and cardiac ejection fraction within normal limits.

Two weeks or longer after any surgical procedure for the gastric carcinoma, estimated life expectancy >3 months and a written consent by the patient or his/

her responsible relative.

Exclusion criteria

Patients thought to have potentially curable disease by surgical resection of the primary tumor, uncontrolled significant co morbid condition, brain or leptomeningeal infiltration, neuropathy≥ grade 1, second malignancy (except non-melanoma skin malignancy) and pregnant or lactating females.

Dose modifications

Chemotherapy was delayed until neutrophils were recovered (>1500/µl) or platelets reached >100000/μl, or until resolution of any significant non-hematological toxicity. Doses of all drugs were reduced by 25% in subsequent cycles in the case of National Cancer Institute-common Toxicity Criteria (NCI-CTC) grade 4 neutropenia or grade 3-4 thrombocytopenia lasting for >3 days, or in the case of febrile neutropenia, which was treated with granulocyte colony-stimulating factor (G-CSF) and antibiotics. The dose of all drugs was reduced by 25% in subsequent cycles in the case of NCI-CTC grade 3-4 mucositis and in the case of poor performance status (over ECOG2). Cisplatin was reduced by 25% when the glomerular filtration rate was between 60 and 40ml/min.

Aim of the work and statistical methods

The primary end point was to compare between the two regimens, DCF and ECF, regarding the progression free survival (PFS) while the secondary end points were the response rate, the overall survival (OS) and toxicity profile. Log-rank test (with two-side 5% significance) was used for comparison between the two arms while Kaplan-Meier method was used to survival rates.

Patients' assessment and evaluation

Before starting treatment, all eligible patients should give complete medical history, must have complete physical examination and lab. Assessment including CBC, liver functions and renal function. The tumor assessment was carried out every two cycles till disease progression or unacceptable toxicity. All radiological measurements of the tumor were assessed by the WHO criteria of response in solid tumors[5] TTP was calculated from the day of randomization till the first evidence of progression or death while the OS was calculated from the day of randomization till death of any cause. Toxicity was graded according to NCI-CTC (common toxicity criteria) version 2[6].

Results

A total number of forty three eligible patients were randomly assigned to receive either DCF (22 patients) or ECF (21 patients). The patients and tumor characteristics for both arms were listed in table 1.

Table 1: Patients and tumor characteristics

Characteristic	Group A (DCF)		Group B (ECF)		P-value
	(No.= 22)	%	(No.= 21)	%	
Sex					
Male	17	77%	18	86%	0.4
Female	5	23%	3	14%	0.6
Age					
Mean	49		52		0.08
Range	45-64		48-65		
ECOG P.S.					
0 and 1	15	68%	16	76%	0.21
2	7	32%	5	24%	0.3
Primary tumor site:					
Gastroesophogeal junction	5	23%	5	24%	0.42
Gastric	17	77%	16	76%	
Disease status:					
Locally advanced	6	27%	5	24%	0.09
Recurrent metastatic	16	73%	16	76%	
Tumor grade					
I	0	0	0	0	0
II	14	64%	15	71%	0.5
III	8	36%	6	29%	0.49
No. of organs involved					
≤2	12	55%	12	57%	0.45
>2	10	45%	9	43%	
Organs involved:					
Stomach	18	82%	17	81%	0.2
LN	16	73%	15	71%	0.45
Liver	13	59%	14	67%	0.33
Peritoneum	7	32%	5	24%	0.08
Others	2	9%	1	5%	0.06
Weight loss ≥5% 3 months before registration	18	82%	16	76%	
Prior therapy					
Surgery					
Curative	7	31.8%	4	19%	
Pariative	4	18.2%	6	28.6%	
Radiotherapy	5	22.7%	3	14.3%	

Group A and group B were found to be comparable and well balanced to each other as regard the initial patients and tumor characteristics with a non significant p value in all criteria.

Total cycles of DCF administered were 93 vs 91 with a median five cycles of DCF (range 2-9) compared to 4 with CEF (range 2-7).

Cycle delays occurred in 64%% DCF vs 57% with CEF, dose-reduction was required in 14 patients with DCF vs 50% with CEF, from those about 80% in both arms, the fluorouracil dose was reduced, due to gastrointestinal toxicities. Neutropenia was the most common adverse event leading to cycle delay in both arms.

The primary end point

Median PFS which was the primary end point was found to be 6 months for group A (DCF) and 4.5 months for group B (ECF) and this difference was statistically significant, p value of 0.035 (with a 95% CI of ratio 0.7841 to 1.883) with a hazard ratio of 0.5609.

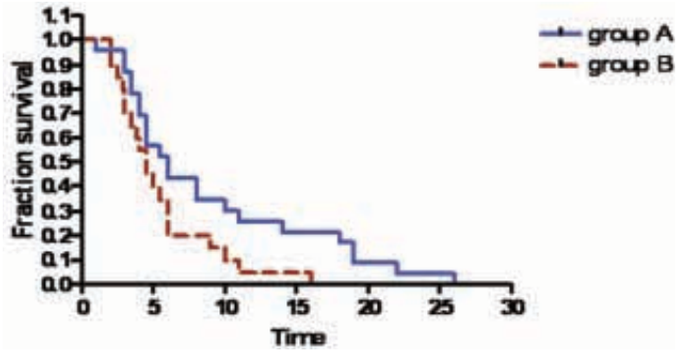

Fig 1: PFS curves of both groups.

The secondary end point

The overall response rate in group A was 36% (8 of 22 pts.) while that in group B was 29% (6 of 21 pts.). Only one patient in group A had complete response, (CR). Partial response, (PR) was detected in 7 (32%) patients of group A *vs* 6 (29%) patients in group B. as shown in table 2. it must be noted here that the statistical difference was so difficult to be calculated due the small number of patients in each group and consequently the *P* value would be biased.

Table 2: Clinical outcome

	Group A (DCF)		Group B (ECF)	
	No	%	No	%
CR	1	5	0	0
PR	7	32	6	29
SD	6	27	7	33
PD	8	36	8	38
ORR	8	36	6	29
Disease control rate	14	63.6	13	61.9

Regarding overall survival:

The median follow up period was 15.7 months, the OS for group A was 8.9 months while that for group B was 8.5 months. The OS rate at one year was 39% for group A and 41% for group B but the differences in both OS and Survival at one year were not statistically significant.

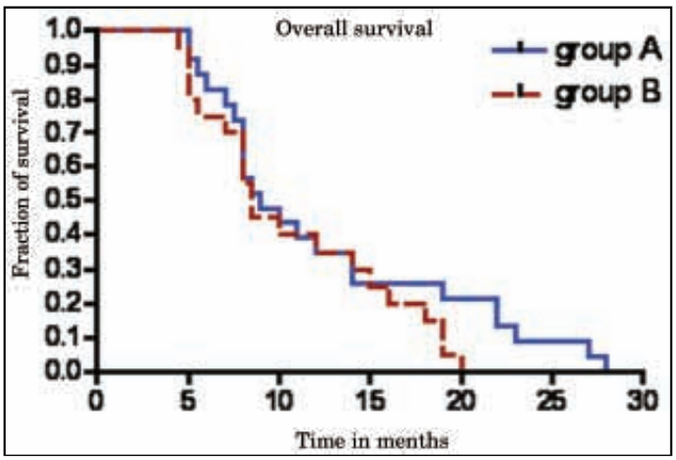

Fig 2: Comparison of overall survival curves.

3- Toxicity:

Both haematologic & non haematologic toxicities, of all grades, are listed in table 3. About 41% in group A had neurotoxicity compared to 28% in group B, grastrointesinal side effects were reported as 22% of group A *vs* 19% of group B had stomatitis. Vomiting and nausea were common toxicities in both arms with 86% in group and 85% in group B.

Regarding the haematologic toxicities neutropenia was more prominent in group A (90%) than group B (85%) with G3 in 22.7% in group A *vs* 19% in arm B neutropenic fever was recorded in 2% in group I, while anaemia was more pronounced in group B (95%) than group A (86%) and in the time that 41% of patients in group A had thrombocytopenia, only 33% of those in group B had this side effect.

Table 3: The haematologic and non haematologic toxicities

Toxicity	Group A (DCF) (n= 22)		Group B (ECF) (n= 21)		P-value
	All grade	G 3+4	All grade	G 3+4	
Non-haematologic					
Fluid retention	2 (9%)	-	-	-	-
Neuropathy	9 (41%)	1(4.5%)	6(28%)	-	0.04
Oral mucositis	5(22%)	2(9%)	4(19%)	2(9.5%)	0.7
Nausea	17(77%)	6(27%)	15(71%)	6(28.5%)	0.06
Vomiting	19(86%)	7(32%)	18(85%)	4(19%)	0.2
Diarrhea	13(59%)	3(13.5%)	10(47%)	3(28.5%)	0.03
Alopecia	20(91%)	1(4.5%)	17(81%)	2(9.5%)	0.8
Haematologic					
Neutropenia	20(90%)	6(27%)	18(85%)	5(23.8%)	0.3
Neutropenic fever	2(9%)	2(9%)	-	-	-
Anaemia	19(86%)	3(13.5%)	20(95%)	2(9.5%)	0.2
Thrombocytopenia	9(41%)	-	7(33%)	1(4.75%)	0.09

Discussion

Despite a myriad of two- and three-drug chemotherapy regimens, there is no consensus about the optimal chemotherapy for advanced gastric cancer. In deciding which therapy is more suitable, we must carefully weigh cost, toxicity, and complexity of administration of therapy with the relative efficacy, quality of life and tolerance in patients. This includes a careful assessment of the individual patient's performance status, burden of comorbid conditions, and age (7).

Modest advances have clearly been made in the development of chemotherapy for advanced gastric cancer. Single agents achieve responses in 10% to 20% of patients with a median survival time of 6 to 7 months, and the index regimen of cisplatin in combination with continuous-infusion fluorouracil (CF) increases response rates to 20% to 30% and median survival time to 7 to 8 months. Phase III trials that add a third agent to CF, including epirubicin plus CF (ECF) and docetaxel plus CF (DCF), report a 10% increase in response rate to 35% to 40% and a 1-month improvement in median survival time to 9 months but at the cost of increasing toxicity[8].

In a randomized phase III study, a regimen consisting of epirubicin, cisplatin, and FU (ECF) showed superior response rates and significantly prolonged survival compared with the historic reference regimen FU, doxorubicin, and methotrexate (FAMTX)[9]. The response rates was 45% *vs* 21% and the median survival was 8.9 *vs* 5.7 months, respectively. Tumor response rate and median survival reached by the ECF combination were reproduced in a second randomized phase III trial including 580 patients; therefore ECF is considered as one of the effective

investigated regimens for gastric cancer and is currently regarded by many as a reference treatment[10].

The combination of docetaxel and cisplatin or docetaxel, cisplatin, and FU (DCF) has been investigated by two multinational study groups, both groups considered FU to contribute significantly to the activity of the regimen[10,11], so both groups have chosen the triple combination of DCF to compare with cisplatin-FU (CF) combinations in ongoing phase III trials[12] Interim results of the American-led trial, which have been recently presented, show a superior response rate of the triple combination DCF compared with CF[11].

Roth et al.[15] compared DCF *vs* ECF in advanced gastric cancer, he reported a randomized phase II comparison of ECF, DC, and DCF. The DCF regimen consisted of a 21-day continuous-infusion FU schedule (similar to ECF) and a higher dose of docetaxel (85mg/m^2) compared with a shorter 5-day infusion of FU and a lower dose of docetaxel (75mg/m^2) in the DCF regimen reported by Van Custem et al.[16] the trial treated a mixture of patients with a performance status of 0 or 1, and the majority of patients (>80%) had distant metastatic disease. Although the phase II design limits a direct comparison of the treatment arms, the three treatment regimens had comparable rate of confirmed response (range, 18% to 37%), time to tumor progression (range, 3.6 to 4.6 months), and median overall survival (range, 8.3 to 10.4 months). Toxicity was substantial in all three arms, with grade 3 or 4 neutropenia observed in 59% of patients treated with ECF and increasing to 76% to 80% of patients treated with either of the docetaxel regimens. The highest rate of febrile neutropenia (41%) was observed in the DCF arm. These results mirror the hematologic toxicity and neutropenic fever reported in other docetaxel combination trials[13-15]. Grade 3 or 4 GI toxicities were highest in the FU-containing DCF arm (15% diarrhea and 7% stomatitis), with comparable rates of nausea and vomiting (18% to 26%) across the three treatment arms.

In our study the median PFS was 6 and 4.5 months for DCF and ECF respectively and this difference was statistically significant to the DCF arm (P=0.035). While the overall survival was comparable in both arms, 8.9 and 8.5 months for group A and group B respectively but this difference was statistically insignificant (P= 0.2). The overall response in DCF arm was 37% and in the ECF arm was 29% and these data were comparable to Roth's study results [15].

When comparing the toxicity in our study the non haematologic toxicities were more evident in the DCF arm Vs. the ECF arm but the difference was statistically insignificant except for neuropathy and diarrhea that were statistically more common in the DCF arm (P value of 0.04 and 0.03 respectively). Regarding the haematologic toxicities, both arms have comparable figures although that neutropenia and thrombocytopenia were more frequent in the DCF arm but the differences were not statistically significant. The toxicity figures are close to those obtained by Van Cutsem and his colleagues[16] especially in the DCF arm with exception of thrombocytopenia that was more frequent in our study (41% *vs* 25%). But this may be due to the difference in the number of patients as Van Custem's study included 227 patients in the DCF arm.

Data from trials of ECF in gastric cancer consistently indicate low rates of GI toxicities for a protracted low-dose infusion of FU. However, the 21-day infusion is cumbersome compared with weekly or biweekly infusion. Oral FU prodrugs, such as capecitabine, substituted for protracted-infusion FU in both the ECF and CF regimens seem to have comparable efficacy, as reported in recent phase III trials. Also it is reported that Epirubicin adds neutropenia, alopecia, and stomatitis to the toxicity of ECF[16]. Many trial have showed the efficacy of the addition of Docetaxel to the widely used doublet regimen CF, of these the V325 phase III study that revealed improvement of the TTP, overall response as well as the survival over CF alone although the population of V325 study had very poor prognosis as 97% of them had metastatic disease and 81% had two or more organs involved[16]. DCF should be considered as one of the effective regimens but the quest of finding a more effective and less toxic combinations must continue. Future replacements of continuous-infusion FU by capecitabine might make this combination even more attractive[17-18].

Conclusion

Both DCF and ECF regimens were tolerable in patients with locally advanced and metastatic gastric adenocarcinoma with acceptable toxicities. The DCF protocol has a significant longer PFS than ECF (P= 0.035) but without significant difference in the OS. both regimens should be considered as effective regimens but the quest of finding a more effective and less toxic combinations must continue. Further studies with larger number of patients, preferably, multicenter studies should be carried out to find out more effective regimens with less toxic with reasonable cost.

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