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Original article

Phase II study of weekly docetaxel, platinum and fluoropyramidine (DCF) in patients with advanced gastric cancer

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Background and aim: The management of advanced gastric cancer (AGC) is challenging with few treatment options available. The aim of this study was to evaluate the efficacy and safety of weekly docetaxel, cisplatin and 5-fluorouracil (DCF) in patients with AGC.
Methods: Nineteen patients with confirmed AGC were enrolled in this study during the period from 2012 to 2015. The DCF regimen consisted of docetaxel 33.3 mg/m2, cisplatin 30 mg/m2 and 5-fluorouracil 1500 mg/m2 over 24-hour continuous intravenous infusion on days 1,8 and 15 every four weeks. The treatment continued for up to 6 cycles as long as there was a response and stopped if there was disease progression or unacceptable toxicities.
Results: Complete response was achieved in only one (5.3%) patient; partial response in twelve (63.15%), stable disease in two (10.6%) and progressive disease in four (21.1%). The progression free survival varied from 3 to 25 months, with a median of 12.5 months.
Conclusion: Weekly DCF in patients with advanced gastric adenocarcinoma was associated with promising results and acceptable toxicity.

Key words: Advanced gastric cancer, Systemic chemotherapy, Docetaxel, Cisplatin, 5-fluorouracil
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INTRODUCTION

Worldwide, gastric cancer is one of the common cancers with a declining incidence over the last decades[1, 2]. In Egypt, there is regional variation in the incidence of gastric cancer[3]. The crude incidence rates / 100.000 population in lower, middle, and upper Egypt for both sexes is 3.7, 2.9 and 4.3 respectively[3].

Like many other solid tumors, the prognosis of early stage gastric cancer is relatively good. However, this early presentation is seen predominantly in Asian countries where early gastric cancer represents 10- 20% of all cases. This is likely to be the result of screening programs in that region. Aiming at cure, the mainstay treatment of gastric cancer is complete resection. Chemotherapy administered peri-operatively or as an adjuvant with or without radiation therapy further improved the 5-year survival to around 40% [4].

The majority (80- 90%) of gastric cancer patients in western countries are either diagnosed in an advanced inoperable stage or develop recurrence within 5 years after curative-intent surgery[5].

The prognosis of advanced gastric cancer (AGC) is dismal with a 5-year survival rate less than 10%. Although there are newly introduced chemotherapeutic regimens and biologic therapies, the median overall survival (OS) of AGC patients continues to be < 1 year[6].

Clinical trials showed that chemotherapy administered with palliative intent is superior to best supportive care in improving the survival of AGC patients and their quality of life[5]. However, these clinical trials recruited patients with relatively better performance status.

Although combination chemotherapy is currently accepted as a treatment for AGC, there is no agreement on the best combination. For example, the combination of docetaxel, cisplatin and 5-fluorouracil (DCF) is a preferred combination in the United States where its administration resulted in improvement of survival[7].

However DCF is of benefit for patients with good performance status due to its associated toxicities. In order to enable its administration to patients with relatively lower performance status, other versions of the DCF regimen had been developed aiming at maintaining efficacy while reducing toxicities[8].

The current study was conducted to determine the overall response rate to weekly DCF and its toxicity in a

cohort of Egyptian AGC patients as well as its impact on progression free survival (PFS).

PATIENTS AND METHODS

Selection of patients

Patients were included in the study when they met the following criteria:

- Age ≥18 years.
- Histologically proven unresectable, recurrent and/or metastatic gastric adenocarcinoma.
- Life expectancy >3 months.
- Adequate laboratory findings: ANC ≥2 X 10^9/L, platelet count ≥80 X 10^9/L, total bilirubin ≤ upper normal limit (UNL), transaminases ≤1.5 times UNL, and creatinine clearance ≥60 ml/min.
- Prior chemotherapy administration was allowed except taxanes.
- Prior radiotherapy administration was allowed.
- Written informed consent was taken from all eligible patients.

Pretreatment evaluation

Included history, physical examination and computed tomography (CT) of chest, abdomen and pelvis. Bone scan and magnetic resonance imaging (MRI) brain with contrast were done when indicated. Routine laboratory tests were done (complete blood picture, urea, creatinine, creatinine clearance, and liver function tests).

Treatment

Docetaxel 33.3 mg/m^2, cisplatin 30 mg/m^2 and 5-fluorouracil 1500 mg/m^2 over 24-hour continuous intravenous infusion on days 1, 8 and 15. Cycle is repeated every 4 weeks and continued for up to 6 cycles.

Treatment was discontinued in case of disease progression or the occurrence of unacceptable toxicities.

Response evaluation

Patients were clinically evaluated every cycle, while CT body chest was done every 3 months.

Evaluation of the response was determined based on modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. Toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.

Statistical methods

The primary end point of this study was the overall response rate. Secondary end points included PFS and the pattern of toxicity.

Chi Square test was used to compare differences in distribution of frequencies among various groups. P value of < 0.05 was considered significant.

PFS was calculated from the time of treatment until the time of disease progression using Kaplan-Meier method[9]

RESULTS

From January 2013 to May 2015, 19 AGC patients were recruited at the Clinical Oncology Department of Assiut University. All patients were examined to sort out those eligible to the study, and all eligible patients were included in the study.

The characteristics of patients are shown in Table 1.

As regard the response to treatment; complete response (CR) was achieved in only one (5.3%) patient; partial response (PR) in twelve (63.2%), stable disease (SD) in two (10.6%), and progressive disease (PD) in four (21.1%).

The relation between the studied variables and response to treatment is shown in Table 2.

Eastern Cooperative Oncology Group (ECOG) performance status and the presence or absence of metastasis were associated with a significant difference in response (p<0.02).

The main toxicities from weekly DCF are shown in Table 3.

There was no life threatening or grade 4 toxicities. The most frequent toxicities were vomiting and neutropenia and were mainly of grade 2.

After a follow up for > 2years; the PFS ranged from 325- months, with a median of 12.5 months (Figure 1).

The mean survival was 24 months in CR patients, 14.65± in PR, 3.5 ± 7 in SD and 3.3 ± 57 in DP (p<0.001).

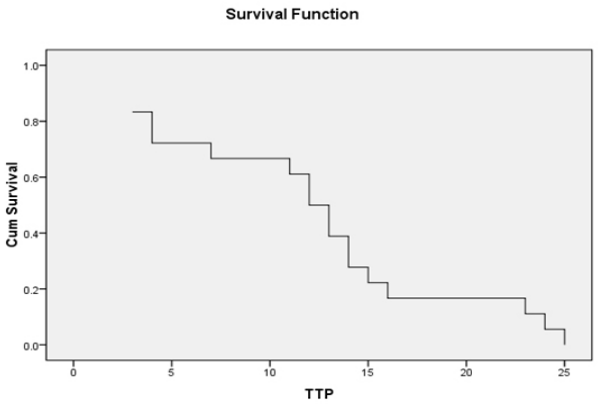

Figure 1: Kaplan Meier curve for PFS of 19 patients with advanced gastric cancer treated with weekly DCF

Table 1: Patients' characteristics

	n.	%
Age		
Median (range)	60 (24-73)	
Sex		
Male	11	57.9
Female	8	42.1
Histologic subtype		
Adenocarcinoma	8	42.1
Signet ring carcinoma	9	47.4
Undifferentiated carcinoma	2	10.5
Histologic grade		
2	4	21.1
3	3	15.8
4	12	63.2
ECOG performance status		
1	5	26.3
2	6	31.6
3	6	31.6
4	2	10.5
Clinical presentation		
Abdominal pain	10	52.6
Weight loss	6	31.6
Gastric outlet obstruction	5	26.3
Vomiting	4	21.1
Gastro-esophageal reflux disease (GERD)	1	5.3
Hematemesis	1	5.3
Increased intracranial pressure	1	5.3
Stage		
Metastatic	8	42.1
Non-metastatic	11	57.9
Site of primary tumor		
Upper part	4	21.1
Middle part	7	36.8
Lower part	7	36.8
> one part	1	5.3
Regularity		
Regular	12	63.2
Irregular	7	36.8
Previous surgery		
No	9	47.4
Radical surgery	7	36.8
Palliative surgery	3	15.8

Table 2: The relation between variables and response

Variable	Response				p value
	CR (*n*=1)	**PR** (*n*=12)	**SD** (*n*=2)	**DP** (*n*=4)	
Age	54	55±13.4	69.5±5	48.3±16.6	0.4
Sex					
Male	1 (100%)	7 (58.3%)	1 (50%)	2 (50%)	0.8
Female	0	5 (41.7%)	1 (50%)	2 (50%)	
ECOG performance status					
1	1 (100%)	4 (33.3%)	0	0	< 0.02
2	0	6 (50%)	0	0	
3	0	2 (16.7%)	2 (100%)	2 (50%)	
4	0	0	0	2 (50%)	
Histologic subtype					
Adenocarcinoma	1 (100%)	5 (41.7%)	1 (50%)	1 (25%)	0.83
Signet ring carcinoma	0	6 (50%)	1 (50%)	2 (50%)	
Undifferentiated carcinoma	0	1 (8.3)	0	1 (25%)	
Histologic grade					
2	0	3 (25%)	1 (50%)	0	0.36
3	1 (100%)	1 (8.3%)	0	1 (25%)	
4	0	8 (66.7%)	1 (50%)	3 (75%)	
Metastases					
No	1 (100%)	7 (58.3%)	0	0	< 0.02
Yes	0	5 (41.6%)	2 (100%)	4 (100%)	
Regularity					
Regular	1 (100%)	8 (66.7)	0	1 (25%)	0.3
Irregular	0	4 (33.3)	2 (100%)	3 (75%)	

Table 3: Toxicities developed in 19 patients treated with weekly DCF

Toxicity type	n.	%
Abdominal pain	1	5.3
Anorexia	1	5.3
Fatigue	2	10.5
Nausea	4	21.1
Neuropathy	9	47.4
Neutropenia	11	57.9
Vomiting	14	73.7
Toxicity grade		
1	2	10.5
2	11	57.9
3	7	36

DISCUSSION

Gastric cancer is the fifth most common cancer in the world in both sexes, after cancers of the lung, breast, colorectum, and prostate. It is the third leading cause of cancer death in both sexes worldwide[10]. Because the majority of patients present in an already advanced stage, gastric cancer remains difficult to cure.

The primary site in this study according to the relationship to long axis of the stomach was more common in the middle and lower parts (36.8% for each), followed by the upper part (21.1%) and combination of more than one part in about (5.3%) and this finding regarding the site was comparable to other studies.

The median age of our patients was 60 years which relatively younger than that reported in other studies in which the median age at diagnosis was 69 years[11]. In our study; males were more commonly affected than females with male to female ratio of 1.4: 1. However, worldwide gastric cancer rates were about twice as high in men as in women[12]. Fifty-eight percent of included patients had metastatic disease which is comparable to that reported in the literature[13]. Adenocarcinoma was the only histologic type confirmed in the present study, with signet ring subtype in 47% of patients, and undifferentiated subtype in 11% of them; however; adenocarcinoma represented about 90 -95% in the World Health Organization classification[14]. This is likely due to the small sample size.

The number of chemotherapeutic drugs used in AGC is increasing and belongs to many classes including taxanes, platinums, fluoropyramidines and others. However, there is no agreement on the best combination regimen of palliative chemotherapy and the overall response is not satisfactory with few patients achieving complete remission. In comparison to best supportive care, combining 5-FU to etoposide / anthracycline + methotrexate improved OS[15]. Combination chemotherapy

regimens containing 5-FU, cisplatin, doxorubicin and mitomycin was found to be superior to single agent 5-FU in randomized clinical trials in terms of response rate and PFS[12].

The efficacy of docetaxel against gastric cancer has been demonstrated in many trials as a single agent with an overall response rate around 20%, in addition to the synergistic effect when added to platinum compounds[16, 17]. However, the toxicity resulting from adding docetaxel to combinations necessitated the search for administration schedules with less toxicity profile and better tolerability, such as weekly administration of docetaxel and the use of granulocyte-macrophage colony-stimulating factor[18].

The DCF regimen was proven to be superior to the combination of cisplatin and 5-FU in the V325 phase III randomized controlled trial in patients with AGC[19]. In that trial, DCF resulted in a higher response rate, longer time to progression and better overall survival[19]. In addition, a positive impact on performance status and quality of life had been demonstrated[20]. However, the DCF regimen has been criticized for its toxicity profile; especially, neurtopenia and neutropenic fever.

In another study that included weekly docetaxel in addition to continuous infusion 5-FU and weekly cisplatin in AGC patients, the overall response rate was 26% [21].

In an attempt to reduce the toxicity resulting from the inclusion of docetaxel in combinations for patients with advanced gastric and esophageal cancer, Ho et al. administered docetaxel at a low weekly dose of 20mg/m^2 combined with cisplatin and 5-FU for 6 weeks and rest for 2 weeks[22]. This was associated with a relatively good response rate (27% PR and 45% SD) with lower rate of hematologic toxicity[21].

The ORR in our study was 68.35% which was higher than previously reported. However, it should be taken into consideration that our study included a small sample size and the lack of comparison to a standard treatment. This better ORR was translated into better PFS (12.5 months). The main toxicities in our study were vomiting (73.7%), neutropenia (57.9%), neuropathy (47.4%), and fatigue (10.5%). grade 2 toxicity was predominant (57.9%), grade 3 in (36.8%), and grade 1 in (10.5%) of patients. no grade 4 was developed.

CONCLUSION

Weekly DCF in Egyptian patients with AGC was associated with promising results and acceptable toxicity. There is a need to be comparing the DCF regimen with standard regimens especially the every 3 weeks DCF.

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