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Clinical evaluation of carcinoembryonic and carbohydrate antigens as cancer biomarkers to monitor palliative chemotherapy in advanced stage gastric cancer

Muhammad Abbas[a,b], Abrar Ahmed[a,b], Ghulam Jilany Khan[c,d,e,*], Mirza Muhammad Faran Ashraf Baig[f], Muhammad Naveed[a], Reyaj Mikrani[a], Tengli Cao[a], Shagufta Naeem[g,*], Meiqi Shi[b,*], Chen Dingding[a,*]

[a] *Department of Clinical Pharmacy, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Jiangsu Province, Nanjing, PR China*
[b] *Department of Oncology, Jiangsu Cancer Hospital, Jiangsu institute of cancer research, Nanjing medical university affiliated cancer hospital Nanjing 210009, Jiangsu, PR China*
[c] *Jiangsu key laboratory of Drug Screening, Evaluation and Pharmacodynamics Research, China Pharmaceutical University, Nanjing, PR China*
[d] *Department of Pharmacology and Therapeutics, Faculty of Pharmacy (FOP), University of Central Punjab, Lahore, Pakistan*
[e] *State Key Laboratory of Bioelectronics, School of Biological Science and Medical Engineering, Southeast University, Nanjing, PR China*
[f] *State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, PR China*
[g] *Department of Pathology, Ayub Medical College, Abbottabad, Pakistan*

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ABSTRACT

Background: Carcinoembryonic antigen (CEA), carbohydrate antigen (CA)-125, CA19-9, and CA72-4 are often found modulated parameters in gastric cancer.
Objective: Our present study is focused to evaluate the synchronization of these biomarkers in response to palliative chemotherapy.

☆ Competing interest: None of authors have any competing interest.
* Corresponding authors.
E-mail addresses: u4574904@hotmail.com (G.J. Khan), drshaguftaanaeem@yahoo.com (S. Naeem), meiqishi1963@163.com (M. Shi), chdd@cpu.edu.cn (C. Dingding).

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Method: A retrospective study was conducted on 216 gastric cancer patients undergoing first-line cisplatin chemotherapy along with antiangiogenic regimen. Blood samples were taken and analyzed biochemically and statistically.
Results: Progression occurred in 78 of 216 patients and the median progression-free survival (PFS) was 5 months. For serum CEA, the median PFS was 4 versus 7 months for elevated and normal groups respectively ($P = 0.01$). The median PFS for normal and elevated CA19-9 and CA72-4 was 6 vs 4 months respectively ($P = 0.001$). In the multivariate Cox regression model, elevated pretreatment level of CEA, CA19-9, and distant metastases were independent factors associated with increased risk of progression ($P = 0.021$, $P = 0.000$, $P = 0.006$, respectively).
Conclusions: Conclusively, elevated pretreatment level of CEA and CA19-9 is correlated with high risk of progression and worse prognosis. Moreover, an additional antiangiogenic therapy is more effective in decreasing cancer biomarker level after palliative chemotherapy that may be correlated with therapeutic triumph.

Introduction

According to statistics, gastric cancer is the fourth most common cancer worldwide and the second most frequent cause of cancer death[1,2] ides, it is estimated that every year gastric cancer is affecting about 1 million people.[3-5] Among these, more than 50% of the cases occur in East Asia, Korea, and Japan having the highest rate of occurrence, with a number of 988,000 new cases in 2008 and 736,000 cancer-related deaths.[1,6-9]

For the patients diagnosed in the early stages, surgery can provide high rates of cure. But, in reality, among the patients with gastric cancer, only 25% or even less of them present to doctor when the disease is in early stage.[10-13] For the rest of the patients, the survival rate is under 50% (in case of nonmetastatic disease stage) and, respectively, below 20% (in the stage at which cancer has already invaded the muscularis propria and there have already occurred regional lymph nodes that make it much harder for patient to recover after gastrectomy).[14-17] Regarding this second type of advanced cancer stage, surgery alone did not prove to give any satisfactory results, the main reason being locoregional and systemic recurrences.[18,19]

Patients diagnosed with extremely advanced gastric cancer may be offered radiotherapy as well as palliative treatment. The results of receiving radiotherapy after surgery are still modest, and it was not proved that it can significantly influence the rate of survival. While palliative method is not a curative treatment, but it plays an extremely important role to improve quality of life, limit complications, and ease pain and at times, prolong life when full recovery from gastric cancer is not possible.[2,20-22]

Tumor markers are small circulating molecules in blood or tissue which are produced by tumor or by host immune cells response to cancer. Measurement of these markers is important in clinical diagnosis, predicting of poor prognosis, and antidrug surveillance.[23-28] The assessment of a particular tumor marker can make a huge difference for the patients in advanced disease stage that will not only help to avoid expensive, time consuming, patient's unresting, un-necessary radiation exposure but also may provide statistically supportive measure to the clinicians to detect and evaluate the progression.[29-33]

Our present study was focused on the clinical utility of tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen (CA)-125, CA19-9, and CA72-4 in advanced stage of gastric cancer patients who had received palliative chemotherapy. We seek to measure whether

Table 1
Chemotherapy regimen for gastric carcinoma.

First-line cisplatin palliative chemotherapy	Dose and cycle
Irinotecan + Cisplatin	Irinotecan 260 mg D1 + Cisplatin 40 mg IV on day 1 every 21
Irinotecan + Raltitrexed	Irinotecan 300 mg D1+ Raltitrexed 5 mg IV on day 1 every 21
Capecitabine + Irinotecan + Oxaliplatin	Capecitabine 1.0 Bid D1-14 + Irinotecan 300 mg D1 + Oxaliplatin 200 mg IV on day 1 every 21
Capecitabine + Docetaxel	Capecitabine 1.5 Bid D1-14 + Docetaxel 120 mg IV on day 1 every 21
S-1 Plus Oxaliplatin	S-1 50 mg Bid D1-14 + Oxa 200 mg IV on day 1 every 21
Paclitaxel + 5-Fluorouracil	Paclitaxel Liposomes 180 mg Iv.Gttq3w + 5-Fu 0.75 g IV on day 1 every 21
Ts-1 Program	Ptx 270 mg D1 + S-1 50 mg Bid IV on day 1 every 21
Cisplatin + Fluorouracil (5fu)	110 mg Iv.Gtt Q3w + 5-Fu 1.5g IV on day 1 every 21
Oxaliplatin + 5 Fluorouracil	Oxaliplatin 200 mg Iv.Gtt D1 + Fluorouracil 2 g IV on day 1 every 21
Docetaxel + Oxaliplatin	Docetaxel 100 mg D1 + Oxaliplatin 150 mg IV on day 1 every 21
Irinotecan + Cisplatin	Irinotecan 260 mg D1 + Cisplatin 40 mg D2-3, 30 mg IV on day 1 every 21
Paclitaxel + Oxaliplatin	Paclitaxel 150 mg D1 + Oxaliplatin 200 mg IV on day 1 every 21
Ptx + Cf + Ft207 + Oxa	Ptx 120 mg D1,5 + Cf0.1 D1-5 + Ft207 0.8 D1-5 + Oxa 190 IV on day 1 every 21
Sox Program	Oxa 200 mg D1, S-1 50 mg Bid on day 1 every 21
Raltitrexed + Oxaplatin	Raltitrexed 5 mg D1, Oxaliplatin 200 mg on day 1 every 21
Raltitrexed + Irinotecan	Raltitrexed 4 mg D1 + Irinotecan 0.3 IV on day 1 every 21
Pemetrexed + Oxaplatin	Pem 0.8 D1 + Oxa 200 mg IV on day 1 every 21
Pemetrexed + Raltitrexed	Ptx 240 mg D1 + Rat 4 mg D1, 21 D/Cycle IV on day 1 every 21

these tumor biomarkers CEA, CA125, CA19-9, and CA72-4 can be of some value to monitor and predict the chemotherapeutic response and efficacy of 2-drugs (platinum-based chemotherapy alone) and 3-drugs (platinum-based chemotherapy plus antiangiogenic agents, ie, [Bevacizumab, Trastuzumab, Nitaluzumab, and Nidotuzumab]) in advanced stages of gastric cancer.

Patients and methods

The study was conducted at department of medical oncology, Jiangsu Cancer Hospital, Nanjing, PR China, which was approved by the Research Ethics Committee on human research of Jiangsu Cancer Hospital. The medical records of 216 patients who underwent first-line chemotherapy from January 2014 to February 2018 at hospital were retrospectively studied. All the patients diagnosed and histologically confirmed with gastric cancer stage IV and had taken palliative chemotherapy were included in the study; Eastern Cooperative Oncology Group routine investigation was 0-2. The Exclusion criteria for patients were those who had coexisting malignant neoplasm of an extra organ and those who had not follow up less than 4 cycles from the initial chemotherapy. All the data were collected until the progression of the tumor, death, or last medical fellow-up.

The assessment to treat patients with palliative chemotherapy was made on the basis of their tumor histology and stage by specialists in gastric oncology, and also monitored that whether patients had the ability to tolerate therapy, and they were treated in accordance with National Comprehensive Cancer Network guidelines.

154 patients have taken first-line cisplatin chemotherapy palliative chemotherapy, ie, Irinotecan + Cisplatin, Irinotecan + Raltitrexed, Capecitabine + Irinotecan + Oxaliplatin, Oxaliplatin + 5-Fluorouracil, Capecitabine + Docetaxel, S-1 plus Oxaliplatin, Paclitaxel + 5-Fluorouracil, Pemetrexed + Oxaliplatin, Cisplatin + Fluorouracil (5FU), Docetaxel + Oxaliplatin, Irinotecan + Cisplatin, Paclitaxel + Oxaliplatin, Docetaxel + Oxaliplatin. While 62 patients have taken platinum-based chemotherapy plus antiangiogenic regimens palliative chemotherapy, ie, BEV + S1, Bevacizumab + Irinotecan, Nidotuzumab + Irinotecan + Cisplatin, Nidotuzumab + Paclitaxel, mFTP + Nidotuzumab, Nilaprozab + Oxaliplatin, Trastuzumab + Irinotecan + Raltitrexed 5 mg D1, Nitaluzumab + Docetaxel + Nedaplatin, Paclitaxel + Raltitrexed + Trastuzumab as mentioned in Tables 1 and 2.[2,34-36]

Table 2
Platinum-based chemotherapy plus antiangiogenic agents palliative chemotherapy-based regimens for patients.

Platinum-based chemotherapy plus anti-angiogenic regimens	Dose and cycle
Bevacizumab + S-1 Plus Oxaplitin	BEV 500 mg D0 + S1 50 mg bid D1-14 (continue Bevacizumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Bevacizumab + Irinotecan	Bevacizumab 500 mg D1 + Irinotecan 0.3 g D114 (continue Bevacizumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Nidotuzumab + Irinotecan + Cisplatin	Nitoximab 400 mg D1 + Irinotecan 280 mg D2 + cisplatin 50 mg D3, 40 mg D4-5 14 (continue nitoximab every 21 d after 4-6 cycles are completed; continue until disease progression)
Nidotuzumab + Paclitaxel	Nitoximab 400 mg D1 + paclitaxel liposomes 150 mg D1 (continue nitoximab every 21 d after 4-6 cycles are completed; continue until disease progression)
mFTP + Nidotuzumab	Paclitaxel liposomes 150 mg D1, 120 mg D5 FT207 1.0 D1-5, OXA 200 mg D2 (continue Nidotuzumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Nilaprozab + Oxaliplatin	Nitoximab 400 mg D1 + oxaliplatin 230 mg D3 (continue nitoximab every 21 d after 4-6 cycles are completed; continue until disease progression)
Trastuzumab + Irinotecan + Raltitrexed	Trastuzumab 440 mg D1 + Irinotecan 0.3 D1 + raltitrexed 5 mg D1 (continue Trastuzumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Nitaluzumab + Docetaxel + Nedaplatin	Nitaluzumab 600 mg D1 + docetaxel 120 mg D1 + nedaplatin 150 mg D1 (continue Nitaluzumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Paclitaxel + Raltitrexed +Trastuzumab	paclitaxel 210 mg iv.gtt q3w + Raltitrexed 4 mg iv.gtt q3w + Trastuzumab 300 mg iv.gtt q3w (continue Trastuzumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Nidotuzumab + Cisplatin	Nitaluzumab 400 mg D1 + 0.5 g D8-9 + cisplatin 20 mg D5-7 (continue Nitaluzumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Nidotuzumab + Paclitaxel	nitoximab 400 mg D1 + paclitaxel 150 mg D2,8 (continue Nidotuzumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Irinotecan + Rituximab	irinotecan 360 mg + rituximab 5 mg (continue Rituximab every 21 d after 4-6 cycles are completed; continue until disease progression)
Nitaluzumab + Docetaxel	nitaluzumab 600 mg D1 + docetaxel 120 mg D1 (continue Nitaluzumab every 21 d after 4-6 cycles are completed; continue until disease progression)
Paclitaxel + Raltitrexed + Trastuzumab	paclitaxel liposomes 210 mg iv.gtt q3w + Raltitrexed 4 mg iv.gtt q3w + Trastuzumab 300 mg iv.gtt q3w (continue Trastuzumab every 21 d after 4-6 cycles are completed; continue until disease progression)

Evaluation of clinical and pathologic response

In our present study, we considered a clinical and pathologic response to evaluate the efficacy of palliative chemotherapy. Clinical responses to palliative chemotherapy were verified by Response Evaluation Criteria in Solid Tumors 1.1,[24] while the pathologic responses to palliative chemotherapy were determined by the criteria defined by Jiangsu Cancer Hospital. Hence, with accordance to the histologic examination of postoperation, board-certified pathologists who specialized in gastrointestinal malignancies examined all specimens.

The aims of this study are to assess progression-free survival (PFS). PFS is the period, whereby the date of receiving chemotherapy to tumor progression or death. Preliminary clinical response to chemotherapy was determined by tomography by means of Response Evaluation Criteria in Solid Tumors response evaluation criteria in solid tumors version 1.1. The following results to be applied in this treatment are classified as complete response (CR), partial response (PR), stable disease (SD), and progression disease. In addition, CR and PR are both defined as the overall response rate; CR, PR, and SD are defined as disease control rate.

Serum assays for CEA, CA125, CA19-9, and CA72-4

Serum samples CEA, CA125, CA19-9, and CA72-4 levels were measured in pre- and post-palliative chemotherapy, respectively. Serum levels of CEA, CA19-9, and CA72-4 were examined with electrochemiluminescence method (E170, Roche Diagnostics, Rotkreuz, Switzerland), and CA125 was assessed with an enzyme-linked immunosorbent assay (ELISA, CA125-ELISA-Kit, CanAg, Gothenburg, Sweden).The cut-off levels were CEA <3.5 ng/mL, CA125 <35 U/mL, CA19-9 <39 U/mL, and CA72-4 <6.9 U/mL as recommended by the manufacturer. The results were indicated positive when the marker serum level was elevated than the cut-off value. Positive combined detection for 4 serum tumor markers was defined as 1 or more serum tumor markers above the cut-off levels.

Statistical analysis

For the analyses, we used SPSS 16.0 for Windows (SPSS Inc, Chicago). Chi-square analysis was used to reveal clinicopathologic topographies and the relationship between tumor markers. Kaplan-Meier method was used for clearly and precisely measure Progression Survival rates, while log-rank test constituted a means to measure statistical differences. Moreover, Cox multivariate investigation was used for evaluating the independent prognostic standards of every tumor marker and clinicopathological characteristics that considerably affect progression. The variances between mean levels of tumor markers before and after receiving palliative chemotherapy were evaluated by *T* test. The Spearman rank order correlations were used to evaluate correlations. The capacity of tumor markers to predict the response to palliative chemotherapy was assessed after applying the receiver-operating characteristics curve. When the *P* value was below 0.05, differences were measured statistically significant.

Results

Patient's characteristics

The sample size of this retrospective analysis of gastric cancer contains 216 patients. The patient's characteristics are mentioned below in Table 3. The data collected for this study had a median age of 55 years (range: 27-91 years) with 132 (61.1%) males and 84 (38.9%) females. According to World Health Organization classification of gastric cancer: 180 (83.33%) were diagnosed Adenocarcinoma, 33 (15.27%) were Squamous cell carcinoma and 3 (1%) were mixed type, 72 (33.34%) were moderately differentiated, 109 (50.46%) poorly and 4 (1.85%) were well differentiated with 154 patients used 2-drugs (conventional platinum-based chemotherapy) and 62 used 3-drugs (conventional platinum-based chemotherapy plus antiangiogenic agents Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab).

Tumor markers and patient's characteristics

Statistical data analysis indicated that pretreatment level of CEA, CA125, CA19-9, and CA72-4 were high in 127 (58.92 %), 54 (25%), 112 (51.78%), and 64 (29.76%) cases, respectively. The correlation between pretreatment tumor markers and patient's characteristics are shown in Table 3.

A significant correlation was found among CEA and age, differentiation, distant metastases and clinical response ($P = 0.023$, $P = 0.001$, $P = 0.006$, $P = 0.001$, respectively). Likewise, a strong correlation was found among CA19-9 and cancer cell differentiation and clinical response ($P = 0.001$, $P = 0.001$, respectively). CA72-4 was correlated only with clinical response ($P = 0.001$). Nevertheless, In Combined positive detection was correlated with clinical response

Table 3
Association of Tumor marker with parameters of patients with gastric cancer.

Variables	Patients (%)	CEA level		CA125 level		CA19-9 Level		CA72-4		Combined	
		Normal	High *P*	Normal	High *P*	Normal	High *P*	Normal	High *P*	Normal	High *P*
Gender		**0.23**		**0.78**		**0.19**		**0.82**		**0.07**	
Male	132 (61.1)	59 (44.7)	73 (55.3)	100 (75.75)	32 (24.24)	68 (51.51)	64 (48.49)	93 (70.45)	39 (29.55)	123 (93.18)	9 (6.82)
Female	84 (38.9)	30 (35.5)	54 (64.5)	62 (73.8)	22 (26.2)	35 (41.66)	49 (58.34)	58 (69.05)	26 (30.95)	71 (84.52)	13 (15.48)
Age		**0.023**		**0.79**		**0.94**		**0.17**		**0.34**	
<60	125 (57.87)	61 (48.8)	64 (51.2)	93 (74.4)	32 (25.6)	61 (48.8)	64 (51.2)	93 (74.4)	32 (25.6)	115 (92)	10 (8)
≥60	91 (42.13)	28 (30.76)	63 (69.24)	69 (75.82)	22 (24.18)	44 (48.35)	47 (51.65)	59 (64.8)	32 (35.2)	79 (86.8)	12 (13.2)
Differentiation		**0.006**		**0.09**		**0.001**		**0.12**		**0.01**	
Moderate	72 (33.34)	40 (55.55)	32 (45.55)	58 (80.55)	14 (19.45)	48 (66.6)	24 (33.4)	53 (73.6)	19 (26.4)	70 (97.2)	2 (2.8)
Poor	109 (50.46)	31 (28.44)	78 (71.56)	77 (70.64)	32 (29.36)	36 (33.02)	73 (66.98)	70 (64.22)	39 (35.88)	89 (81.65)	20 (18.35)
Others	4 (1.85)	1 (25)	3 (75)	3 (75)	1 (25)	3 (75)	1 (25)	3 (75)	1 (25)	4 (100.0)	0 (00)
Missing	31 (14.35)	17 (54.8)	14 (45.2)	24 (77.4)	7 (22.6)	18 (58.06)	13 (41.94)	26 (83.8)	5 (16.2)	31 (100.0)	0 (00)
Distant metastasis		**0.001**		**0.20**		**0.20**		**0.31**		**0.06**	
Yes	118 (54.62)	32 (27.11)	86 (72.89)	85 (72.03)	33 (27.97)	52 (44.06)	66 (55.94)	80 (67.8)	38 (32.2)	101 (85.59)	17 (14.41)
No	98 (45.38)	57 (58.16)	41 (41.84)	77 (78.57)	21 (21.43)	52 (53.06)	46 (46.94)	72 (73.47)	26 (26.53)	93 (94.89)	5 (5.11)
Clinical Response		**0.001**		**0.07**		**0.001**		**0.001**		**0.001**	
PR + SD	138 (63.88)	84 (60.87)	54 (39.13)	111 (80.43)	27 (19.57)	99 (71.74)	39 (28.26)	122 (88.4)	16 (11.6)	138 (100.0)	0 (00)
PD	78 (36.11)	5 (6.41)	73 (93.59)	51 (65.38)	27 (34.62)	5 (6.41)	73 (93.59)	29 (37.18)	49 (62.82)	54 (69.23)	24 (30.77)
Histological type		**0.13**		**0.69**		**0.18**		**0.1**		**0.59**	
Adenocarcinoma	180 (83.33)	69 (38.33)	111 (61.67)	134 (74.44)	46 (25.56)	82 (45.56)	98 (54.44)	131 (72.8)	49 (27.2)	163 (90.56)	17 (9.44)
Squamous cell	33 (15.27)	16 (48.48)	17 (51.52)	25 (75.76)	8 (24.24)	19 (57.58)	14 (42.42)	18 (54.55)	15 (45.45)	28 (84.85)	5 (15.15)
Others	3 (1)	3 (100.0)	0 (00)	3 (100.0)	0 (00)	3 (100.0)	0 (00)	3 (100.0)	0 (00)	3 (100.0)	0 (00)
Treatment		**0.92**		**0.69**		**0.96**		**0.63**		**0.23**	
2-drugs	154 (71.29)	63 (40.9)	91 (59.1)	117 (75.97)	37 (24.93)	74 (48.05)	80 (51.95)	107 (69.48)	47 (30.52)	141 (91.56)	13 (8.44)
3-drugs	62 (28.71)	26 (41.94)	36 (58.06)	45 (72.58)	17 (27.42)	30 (48.39)	32 (51.61)	45 (72.58)	17 (27.42)	53 (85.48)	9 (14.52)

Bold values are statistically significant ($P < 0.05$); **PR**, partial response; **SD**, stable disease; **PD**, disease progression;**2-drugs**, conventional platinum-based chemotherapy;**3-drugs**, conventional platinum-based chemotherapy plus anti-angiogenic agents therapy.

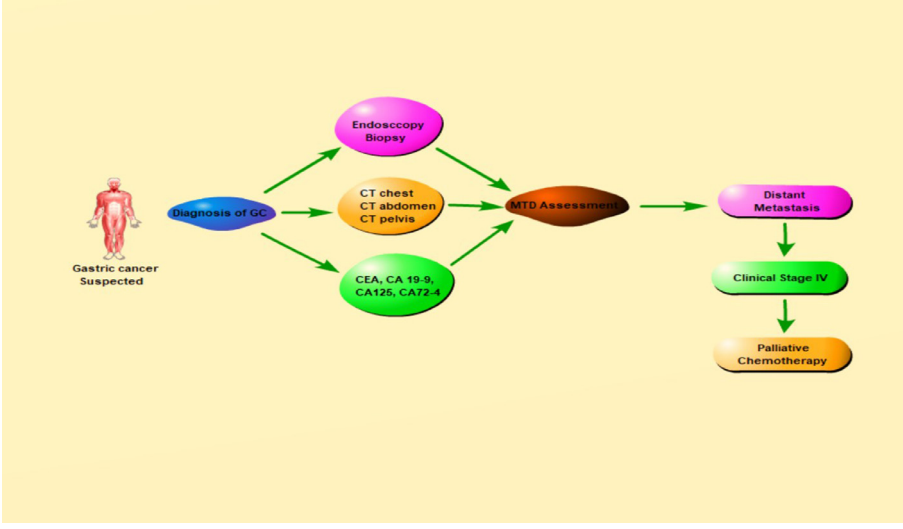

Fig. 1. The management of patients with gastric cancer in palliative care.

Table 4
Multivariate analysis for progression-free survival.

Variables	HR	95% CI	*P*
Age: <60 Y vs ≥60	0.718	0.399-1.240	0.210
Sex: Male vs Female	1.021	0.618-1.698	0.967
Treatment: 2- vs 3-drugs	0.492	0.240-1.001	0.049
Distant Metastases: Yes vs No	3.304	1.400-7.797	**0.006**
CEA: ≤3.5 ng/mL vs >3.5 ng/mL	3.541	1.207-10.385	**0.021**
CA19-9: ≤39 U/mL vs > 39 U/mL	6.855	23.34-20.128	**0.000**
CA72-4: ≤16.3 U/mL vs >16.3 U/mL	1.556	0.895-2.810	0.147

2-drugs represent conventional platinum-based chemotherapy; 3-drugs represent conventional platinum-based chemotherapy plus anti-angiogenic agents. Bold values are statistically significant ($P < 0.05$).

and cancer cell differentiation ($P = 0.001$, $P = 0.01$, respectively). Hence, there was no correlation found among CA125 and patient's characteristics ($P > 0.05$; Fig 1).

Associations of tumor markers with PFS

Our studies showed that progression occurred in 78 of 216 patients, in which 64 (81.96%) were using 2-drugs and 14 (18.03%) patients were using 3-drugs therapy. Overall median PFS was 5 months. Patients with high and normal CEA levels presented median PFS of 4 vs 7 months ($P = 0.01$). Likewise, patients with high and normal CA19-9 and CA72-4 had median PFS of 4 vs 6 ($P = 0.001$). Though, the level of CA125 was not associated with PFS ($P > 0.05$; Table 4). It was observed that patients with high pretreatment level of CEA, CA19-9, and CA72-4 were associated with less PFS to normal level (Fig 2).

Moreover, the Cox regression analysis was performed to assess the potential of these biomarkers as an independent predictor of PFS in gastric cancer.

Furthermore, to assess the prognostic values of combination of the tumor markers, we found 5 different groups of patients, including 71 patients (32.73%) with 1 high biomarker, 33 patients (15.47%) with 2 higher biomarkers, 44 patients (20.23%) with 3 higher, and 22 patients (10.11%) with 4 higher biomarkers whereas 46 (21.42%) patients were observed with normal pretreatment level in all the biomarkers. Upon comparison of PFS based on these of all these 4 tumor markers,

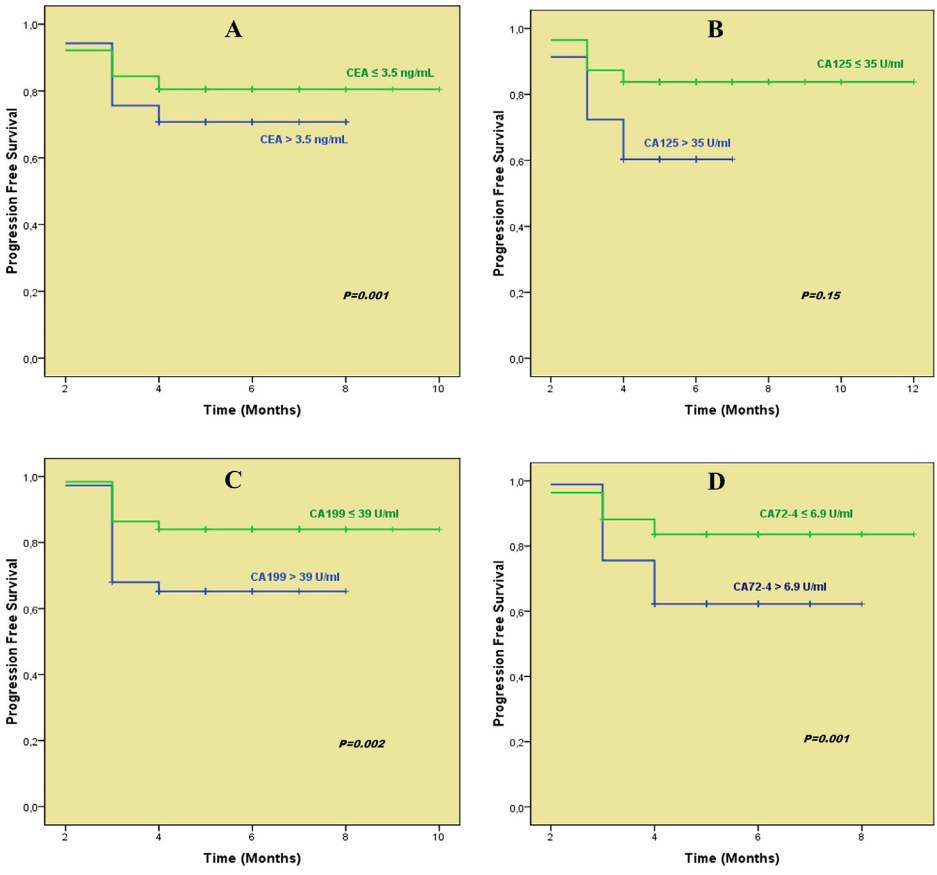

Fig. 2. Kaplan-Meier progression-free survival (A-D) according to CEA, CA19-9, and CA72-4 normal and high serum level, respectively. High serum level is associated with decreased PFS except for CA125. CA, carcinoembryonic antigen; CEA, carbohydrate antigen; PFS, progression-free survival.

patients with 4 higher tumor markers presented significantly less PFS than patients with normal tumor marker level prior to treatment (Fig 3A, $P \leq 0.001$).

Association of treatment with PFS

In our present study, 154 patients (71.29%) were treated with 2-drugs (first-line platinum-based chemotherapy) therapy whereas 62 patients (28.71%) received 3-drugs therapy (first-line platinum-based chemotherapy and antiangiogenic agents (Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab). Upon the comparison of PFS based on the therapeutic regime, we found that patients who were taking 3-drugs therapy had prolonged survival while those who received 2-drugs therapy had a poor prognosis and shorter PFS (Fig 3B, $P = 0.002$; Fig 4).

Changes of tumor markers and correlation with response to palliative chemotherapy

All the patients (216) were treated with palliative chemotherapy and the clinical response was PR in 111 (51.19%), SD in 27 (12.50%), and progression of disease in 78 (36.11%) patients. Pa-

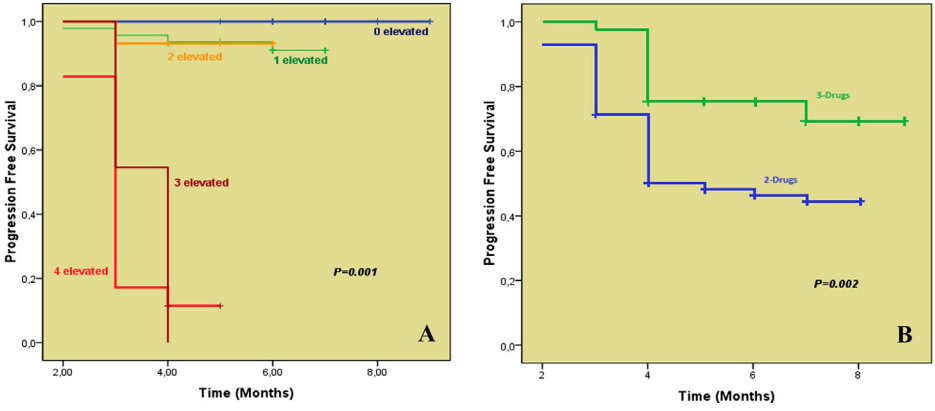

Fig. 3. Kaplan-Meier progression-free survival. (A) Combination of 4 biomarkers. (B) Comparison between 2-drugs (conventional platinum-based chemotherapy) and 3-drugs (conventional platinum-based chemotherapy+ antiangiogenic agents).

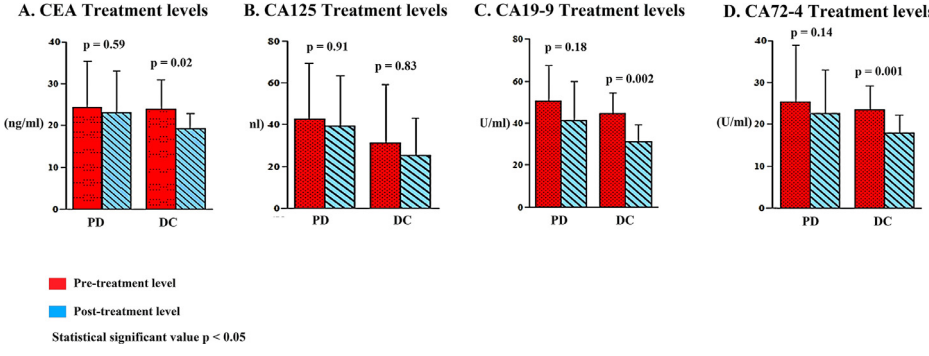

Fig. 4. Mean levels of biomarkers before and after palliative chemotherapy in disease control (CR + PR + SD) and PD (disease progression) group respectively. CEA, CA19-9, and CA72-4 decreased more significantly in the disease control (CR + PR + SD) group than the disease progression (PD) group ($P = 0.02$, $P = 0.002$, and $P = 0.001$, respectively). CA125 decrease was not statistically significant ($P > 0.05$). CR, complete response; PD, progression disease; PR, partial response; SD, stable disease.

tients experienced side effects; abdomen pain, alopecia, anorexia, anemia, bone marrow depression, diarrhea, nausea, thrombocytopenia, and vomiting. Eventually none of the patients expired during the treatment.

The levels of all biomarkers were recorded at baseline and after fourth cycle of palliative chemotherapy respectively. The mean level of CEA, CA19-9, and CA72-4 were found decreased significantly after palliative chemotherapy ($P = 0.0062$, $P = 0.001$, $P = 0.002$) especially in the diseased control group compare to disease progression group ($P = 0.03$, $P = 0.001$, $P = 0.002$ respectively). Moreover, we have also compared the response of chemotherapy in patients receiving 2-drugs and 3-drugs therapies. We found that patients were more responsive to 3-drugs therapy as compared with 2-dugs. To justify the outcomes, we have compared pretreatment and after treatment tumor markers level and indicated significant decrease in the tumor markers level of patients receiving 3-drugs therapy ($P = 0.005$, $P = 0.0006$, $P = 0.001$ for CEA, CA19-9, and CA72-4, respectively) compared with patients with 2-drugs therapy ($P = 0.09$, $P = 0.0002$, $P = 0.09$ for CEA, CA19-9, and CA72-4, respectively).

Discussion

In advanced stage of gastric carcinoma, the role of platinum-based chemotherapy has been established for two decades.[2,37-39] However, in recent years, antiangiogenic agents, ie, (Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab) have also shown efficacy in several solid tumors and may provide additional benefits for advanced stage gastric cancer in addition to standard first-line platinum-based therapy.[34-36,40-42] Earlier studies have confirmed the safety and efficacy of antiangiogenic agents, ie, (Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab), when combined with platinum-based (Paclitaxel/carboplatin) chemotherapy with increased survival rates in previously untreated patients with gastric cancer.[43-47] In present study, Patients who used 3-drugs regimen antiangiogenic agents, ie, (Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab + first-line platinum-based chemotherapy) were found with relatively greater PFS (median PFS was 7 months) compared with patients used 2-drugs regimen (first-line platinum-based chemotherapy; median PFS was 4 months; $P = 0.002$) and these findings are consistent with earlier studies.[37,48] The synergistic effect of antiangiogenic agents with platinum-based (Paclitaxel/carboplatin) therapy could be a reason of improving patient quality of life.[45,49]

To find out the correlation between pretreatment status of tumor markers and different parameters, we performed a chi-square test and found that CEA positivity/high pretreatment level was associated with age of the patient, differentiation, distant metastases, and clinical response. CA19-9 was correlated with differentiation and clinical response while CA72-4 was correlated with clinical response only. In our results, we also found that positivity of more than 1 biomarker (combined detection) is associated with differentiation and clinical response to chemotherapy.

CEA is a nonspecific biomarker with abnormal expression in several solid tumors including gastric cancer. Contradictory results concerning the prognostic effect of pretreatment CEA level have been reported.[50-52] In our results, patients with high pretreatment serum CEA level were associated with shorter PFS and worse prognosis compared with patients having a normal level, consistent with the results in previous studies.[53,54] Furthermore, in multivariable Cox regression model, CEA was found to be an independent factor associated with PFS.

The role of CA19-9 and CA72-4 is not well elucidated.[53,54] Some studies found its prognostic value in surgically treated patients.[29,55-57] Our studies have shown that the high serum CA19-9 had a significant effect on prognosis and could be used as an independent factor in poor prognosis (multivariable Cox regression model).

Previous study did not find any correlation of CA125 with PFS in gastric cancer patients.[29] However, in our results, the difference in the PFS between high and normal pretreatment levels of CA125 was also not significant ($P > 0.05$). The value of CA72-4 is controversial in gastric cancer; however, in adenocarcinoma CA72-4 is widely accepted.[54]

The relationship between tumor markers and response to chemotherapy in breast, colorectal, ovarian, and pancreatic cancer has already been reported[9,58]; however, the significance of such tumor markers in the advanced stage of gastric cancer has not been explored thoroughly from clinical aspect.[54,59]

Our present study with a special focus on tumor biomarker response to palliative therapy, the mean level of tumor markers became significantly lower after palliative chemotherapy. The decrease in the mean level of CEA, CA19-9, and CA72-4 attain statistical significance ($P = 0.02$, $P = 0.002$, $P = 0.001$, respectively) as compared with the disease progression group.

A previous study of first-line chemotherapy with or without antiangiogenic agents (Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab) supports the hypothesis that antiangiogenic agents, ie, (Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab) improve drug delivery to the tumor.[60-62] Our present study for the comparison of effective association of biomarkers with 2-drugs (first-line platinum-based therapy) and 3-drugs antiangiogenic agents, ie, (Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab + Paclitaxel, carboplatin) regimens, we have found a significant decrease in the mean level of tumor markers CEA, CA19-9, and CA72-4 of patients using 3-drugs regimen as compare to patients taking 2-drugs regimen. Taken together,

these findings suggest that an appropriate addition of antiangiogenic agent, ie, (Bevacizumab, Trastuzumab, Nitaluzumab, Nidotuzumab) to first-line platinum-based chemotherapy may improve PFS as well as quality of life of cancer patients.

Although these biomarkers CEA, CA125, CA19-9, and CA 72-4 may not be an appropriate prognostic measure at individual level however a combination of these biomarkers may assist in the assessment of therapeutic and diagnostic measure of gastric cancer in advanced stage IV.[63] Chiu et al reported in their study that the changes occurring in tumor markers (combination of CEA, CA125, and CA19-9) pre– and post–gefitinib-based chemotherapy) were in relation to tumor response and PFS,[64] additionally serum CEA levels were found closely associated with advanced stage IV gastric cancer as promising biomarkers.[65] So, the usage of tumor marker scores might play a promising role in diagnosis and in forecasting the outcome of gastric cancer in advanced stage IV.[7,29,40,66]

Current study highlights the combined positive detection (when 1 or more tumor markers are above the cut-off value) was associated with differentiation and clinical response and when analyzed by Kaplan-Meier survival curve. We have found a significant decrease in the PFS of patients having 3 and/or 4 tumor markers elevated (pretreatment) compared with those patients having 0, 1, and/or 2 tumor markers elevated (pretreatment). And patients with more than 2 high pretreatment tumor markers were less responsive to chemotherapy even if they were treated with 3-drugs regimen. Thus, oncologists should consider the value of these biomarkers before starting chemotherapy and prescribe a suitable combination of chemotherapy,[7,40,67] analyzed by Kaplan-Meier survival curve. We have found a significant decrease in the PFS of patients having 3 and/or 4 tumor markers elevated (pretreatment) compared with those patients having 0, 1, and/or 2 tumor markers elevated (pretreatment). And patients with more than 2 high pretreatment tumor markers were less responsive to chemotherapy even if they were treated with 3-drugs regimen. Thus, oncologists should consider the value of these biomarkers before starting chemotherapy and prescribe a suitable combination of chemotherapy.[23,68]

Conclusions

Conclusively, integrated prognostic data, including the CEA, CA19-9, and CA72-4 biomarkers, might be useful in monitoring chemotherapeutic response and prediction of prognosis in advanced stage gastric cancer patients using palliative chemotherapy. Also, an addition of antiangiogenic therapy is more effective in decreasing cancer biomarker level after palliative chemotherapy that improves patient quality of life. Moreover, a prospective study with wider number of patients and regions may be required for further endorsement of our findings.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.08.003.

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