The efficacy of modified docetaxel-cisplatin-5-fluorouracil regimen as first-line treatment in patients with alpha-fetoprotein producing gastric carcinoma

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ABSTRACT

Alpha-fetoprotein producing gastric carcinoma (AFP-PGC) is a rare cancer for which limited data on the clinicopathological features and treatment modalities exist. The aim of this study was to compare the efficacy of modified docetaxel-cisplatin-5-fluorouracil (mDCF) as the first-line chemotherapy regimen in metastatic AFP-PGC and non-AFP-PGC. The patients diagnosed with metastatic gastric cancer who were given mDCF as first-line therapy were retrospectively reviewed. The patients with a basal serum AFP level over 9 ng/ml were defined as AFP-PGC patients. In total, 169 patients (34 with AFP-PGC and 135 with non-AFP-PGC) were included in this study. AFP-PGC patients had more liver metastases than non-AFP-PGC patients ($p < 0.001$). A decrease in basal AFP levels after three cycles of chemotherapy was significantly different in AFP-PGC group ($p = 0.001$). Overall disease control rate was 79.4% (partial response [PR] - 44.1%, stable disease [SD] - 35.3%), and 82.2% (complete response - 3%, PR - 36.2%, SD - 43%) in AFP-PGC and non-AFP-PGC patients, respectively. There was no difference between AFP-PGC and non-AFP-PGC groups in overall and progression-free survival rates (11.3 versus 11.4 months and 7.7 versus 7.1 months, respectively). Rates of grade 3-4 hematologic toxicity were 8.8% and 6.7% for neutropenia in AFP-PGC and non-AFP-PGC group, respectively and 5.9% and 7.4% for anemia. In conclusion, mDCF regimen is well-tolerated with acceptable toxicity outcomes in both AFP-PGC and non-AFP-PGC patients. A statistically significant decrease in AFP levels after mDCF regimen indicate that AFP might be considered as a supplemental marker of response to mDCF chemotherapy in AFP-PGC patients. However, further prospective clinical trials are required in this area.

KEY WORDS: Alpha-fetoprotein; alpha-fetoprotein producing gastric carcinoma; gastric carcinoma; modified docetaxel-cisplatin-5-fluorouracil; chemotherapy

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INTRODUCTION

Alpha-fetoprotein (AFP) is a glycoprotein which is predominantly secreted by the fetal yolk sac and liver during the gestational period [1]. It is used as a tumor marker in hepatocellular carcinoma and germ cell tumors (i.e., yolk sac tumor), in addition to the increased levels of AFP in benign processes such as chronic liver disease, viral hepatitis, and cirrhosis [2-5]. AFP may also be increased in some solid tumors such as gastric carcinoma [6-8]. However, the underlying mechanism is unclear.

AFP producing gastric carcinoma (AFP-PGC) constitutes 2.7-8% of all gastric cancers with high proliferation index, low apoptotic rate, and increased neovascularization [9]. Therefore, the patients with AFP-PGC tend to have more frequent liver metastases, advanced-stage disease, and poor prognosis at presentation [9-13].

Due to the rarity of this cancer, there is limited data in the literature on the clinicopathological features of AFP-PGC and treatment modalities. In this study, we aimed to evaluate the efficacy of modified docetaxel-cisplatin-5-fluorouracil (mDCF) regimen as a first-line setting for the patients with AFP-PGC in comparison to non-AFP-PGC patients. We also evaluated the prognostic significance of AFP as a supplemental marker of response to mDCF chemotherapy in AFP-PGC patients.

MATERIALS AND METHODS

Patients

The medical records of patients with histopathologically confirmed diagnosis of gastric cancer between 2009 and 2015, were evaluated retrospectively. The cut-off

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value for AFP was defined as 9 ng/mL (normal range = 0-9 ng/mL) according to the UNICEL DXI 600-800 assay (Beckman Coulter immunoassay dx800). Therefore, AFP level higher than 9 ng/mL (>9 ng/mL) was accepted as "high" AFP level. According to AFP levels, the metastatic gastric cancer patients were classified into two groups: AFP-PGC group - patients with high AFP level (>9 ng/mL) at diagnosis and non-AFP-PGC group - patients with normal serum AFP levels (AFP <9 ng/mL). The exclusion criteria were other causes of high AFP levels such as chronic liver disease, yolk sac tumor, teratoma, cirrhosis, or hepatocellular carcinoma. mDCF is the preffered first-line chemotherapy regimen in patients with advanced gastric cancer at our clinic. In addition, previous reports showed the efficacy of mDCF regimen in these patients [14-16]. Thus, all patients in this study had first-line mDCF regimen (docetaxel 60 mg/m^2/day [day 1], cisplatin 60 mg/m^2/day [day 1], 5-fluorouracil 600 mg/m^2/day [days 1-5], every 3 weeks). Tumor markers (AFP, carcinoembryonic antigen [CEA], carbohydrate antigen 19-9 or cancer antigen 19-9 [Ca 19-9]) were evaluated at diagnosis and after the third cycle of chemotherapy. Clinicopathological characteristics and survival outcomes were evaluated retrospectively for all patients. Treatment response was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.1).

Statistical analysis

Statistical Package for the Social Sciences version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and $p \leq 0.05$ was considered as statistically significant. For descriptive statistics, categorical variables were presented as frequency distributions and percentages, and continuous variables as medians, minimum and maximum values. Categorical variables were analyzed using the Chi-square or Fisher's exact test. Mann–Whitney U test was used for the non-parametric data. The Wilcoxon test was used to detect the change in AFP level. Survival analysis was performed according to Kaplan–Meier method, whereas log-rank statistics was used to compare the subgroups. The overall survival (OS) was defined as the time from the start of chemotherapy to death or date last known alive. Progression-free survival (PFS) was defined as the time from the start of chemotherapy to the first disease recurrence or the last follow-up.

RESULTS

A total of 169 metastatic gastric cancer patients who were given mDCF as first-line therapy were evaluated. Thirty four patients had high AFP levels at diagnosis. The clinicopathological features of AFP-PGC patients and non-AFP-PGC patients are shown in Table 1. The median age was 54 years (range: 22-77) and 57 years (range: 26-73) in AFP-PGC and non-AFP-PGC groups, respectively. Most of the patients were male in both groups (76% and 70%, respectively). There was no significant difference between these two groups in terms of age, sex, smoking history, comorbidities, Eastern Cooperative Oncology Group performance status, tumor location, weight loss, Lauren classification, lymphovascular invasion, perineural invasion, and site of extrahepatic metastasis; but we found statistically significant differences in liver metastasis and operation rates ($p < 0.05$).

TABLE 1. Demographic characteristics of patients with AFP-PGC and non-AFP-PGC

Characteristics	AFP-PGC (%) n=34	Non-AFP-PGC (%) n=135	*p* value
Age, median (range)	54 (22-77)	57 (26-73)	0.85
Sex			
Female	8 (23.5)	40 (29.6)	0.40
Male	26 (76.5)	95 (70.4)	
Smoking history	24 (70.6)	82 (60.7)	0.28
Comorbidity	12 (35.3)	58 (43)	0.41
ECOG performance status			0.72
0-1	26 (76.5)	107 (79.3)	
2	8 (23.5)	28 (20.7)	
Weight loss			
Yes	14 (41.2)	63 (46.7)	0.56
No	20 (58.8)	72 (53.3)	
Lauren classification			
Diffuse	9 (34.6)	59 (44.7)	0.63
Intestinal	10 (38.5)	44 (33.3)	
Mixed	7 (26.9)	29 (22.0)	
Tumor location			
Fundus, cardia	15 (44.1)	56 (41.5)	0.93
Corpus	11 (32.4)	48 (35.5)	
Antrum	8 (23.5)	31 (23.0)	
Bormann's classification			
Type I-II	5 (14.7)	25 (18.5)	0.60
Type III-IV	29 (85.3)	110 (81.5)	
LVI			
Yes	18 (78.3)	68 (66.0)	0.25
No	5 (21.7)	35 (34.0)	
PNI			
Yes	18 (78.3)	67 (65.0)	0.22
No	5 (21.7)	36 (35.0)	
Surgery			
Yes	9 (26.5)	72 (53.3)	0.005
No	25 (73.5)	63 (46.7)	
Metastatic regions			
Liver	24 (70.6)	43 (31.9)	<0.001
Peritoneum	4 (11.8)	36 (26.7)	0.06
Lung	5 (14.7)	10 (7.4)	0.18
Distant lymph node	9 (26.5)	32 (23.7)	0.73
Bone	4 (11.8)	8 (5.9)	0.26
Others	3 (8)	31 (23.0)	0.06

AFP-PGC: Alpha-fetoprotein producing gastric carcinoma; ECOG: The Eastern Cooperative Oncology Group; LVI: Lymphovascular invasion; PNI: Perineural invasion

TABLE 2. Laboratory values for tumor markers in AFP-PGC group

Tumor markers	Normal range	Basal (Median, range)	After third chemotherapy cycle (Median, range)	*p* value
AFP (ng/mL)	0-9	118.5 (10.1-19702)	48.0 (2.3-1989)	0.001
CEA (ng/mL)	0-3	87.5 (1.7-1500)	12 (1.4-1393)	0.101
Ca 19-9 (IU/mL)	0-35	14.8 (0.8-1959)	11.2 (0.8-130)	0.272

AFP-PGC: Alpha-fetoprotein producing gastric carcinoma; CEA: Carcinoembryonic antigen; Ca 19-9: Carbohydrate antigen 19-9

All of the patients had palliative first-line mDCF regimen with a median of 6 cycles (range: 2-10). In AFP-PGC group, the basal median AFP level was significantly decreased after the third cycle of mDCF regimen (p = 0.001), compared to non-AFP-PGC group. However, the decrease in CEA and Ca 19-9 levels after the third cycle of mDCF was not statistically significant (Table 2). None of our patients with AFP-PGC had complete response (CR), however the overall disease control rate was 79.4% (partial response [PR] (44.1%), stable disease [SD] (35.3%)). Seven patients had progression of the cancer. The overall disease control rate in non-AFP-PGC group was 82.2% [CR (3%), PR (36.2%), SD (43%)] (Table 3). Treatment-related grade 3-4 toxicities are shown in Table 4. The most common grade 3-4 hematologic and non-hematologic toxicities were neutropenia and nausea/vomiting in all patients. Grade 3-4 neutropenia and anemia were reported as hematologic toxicities in both groups (8.8% versus 6.7% and 5.9% versus 7.4%, respectively). While the rate of nausea/vomiting as grade 3-4 non-hematologic toxicity was 11.8% in AFP-PGC group, it was 12.6% in non-AFP-PGC group. None of our patients had primary granulocyte colony-stimulating factor (G-CSF) prophylaxis. Three patients (8.8%) in AFP-PGC group and 13 patients (9.6%) in non-AFP-PGC group had chemotherapy delays. Dose reduction was performed in 2 patients (5.9%) in AFP-PGC group and in 11 patients (8.1%) in non-AFP-PGC group, because of grade 3-4 hematologic and non-hematologic adverse events. No toxic death was reported in both groups (Table 4).

In all patients, the median follow-up was 10.5 months (range: 1.5-23.5). The median OS and PFS were 11.3 months (95% confidence interval [CI]: 10.2-12.4) and 7.1 months (95% CI: 6.6-7.7), respectively. In AFP-PGC patients, the median OS and PFS were 11.3 months (95% CI: 8.0-14.7) and 7.7 months (95% CI: 5.7-9.7), whereas they were 11.4 months (95% CI: 10.2-12.5) and 7.1 months (95% CI: 6.6-7.6) in non-AFP-PGC group. These differences were not statistically significant [p = 0.40, p = 0.46, respectively] (Figures 1 and 2). Second-line chemotherapy was given to 16 patients (47%) in AFP-PGC and to 72 patients (53.3%) in non-AFP-PGC group because of the disease progression. EOX regimen [Epirubicin 50 mg/m²/day (day 1), oxaliplatin 130 mg/m²/day (day 1), capecitabine 2 × 1000 mg/m²/day (days 1-14), every 3 weeks] was most commonly used as second-line chemotherapy (in 12 AFP-PGC patients and 39 non-AFP-PGC patients).

TABLE 3. Response to first line mDCF regimen

Best response to mDCF	AFP-PGC (%) n=34	Non-AFP-PGC (%) n=135
CR	-	4 (3.0)
PR	15 (44.1)	49 (36.3)
SD	12 (35.3)	58 (43.0)
Progressive Disease	7 (20.6)	24 (17.8)

AFP-PGC: Alpha-fetoprotein producing gastric carcinoma; CR: Complete response, PR: Partial response, SD: Stable disease, mDCF: Modified docetaxel-cisplatin-5-fluorouracil

TABLE 4. Treatment-related toxicity

Adverse events	AFP-PGC (%)	Non-AFP-PGC (%)
Dose reduction	5.9	8.1
Course delay	8.8	9.6
Grade 3-4 toxicity		
Neutropenia	8.8	6.7
Anemia	5.9	7.4
Thrombocytopenia	2.9	2.2
Nausea and vomiting	11.8	12.6
Mucositis	-	2.2
Diarrhea	-	1.5

AFP-PGC: Alpha-fetoprotein producing gastric carcinoma

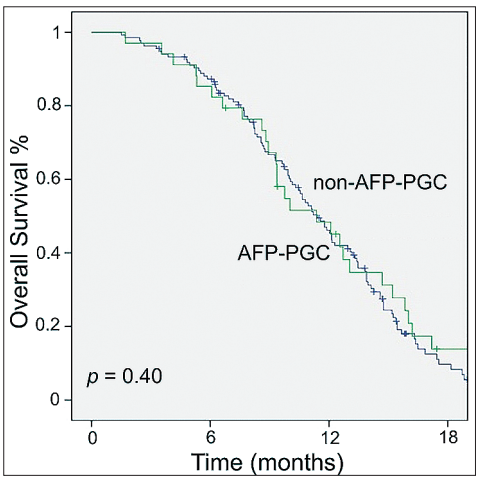

FIGURE 1. Overall survival of metastatic alpha-fetoprotein producing gastric carcinoma (AFP-PGC) and non-AFP-PGC with modified docetaxel-cisplatin-5-fluorouracil regimen. The median overall survival was 11.3 months (95% confidence interval [CI]: 8.0-14.7) for AFP-PGC and 11.4 months (95% CI: 10.2-12.5) for non-AFP-PGC patients (p = 0.40).

DISCUSSION

The prevalence of AFP-PGC differs according to the geographical locations. Although gastric cancer is more common in Eastern countries such as Japan and Korea, AFP-PGC

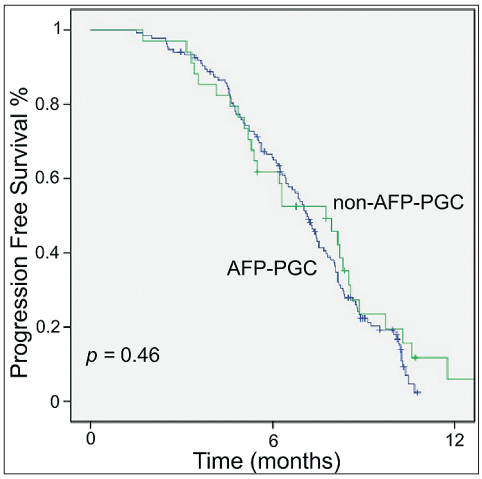

FIGURE 2. Progression-free survival of metastatic alpha-fetoprotein producing gastric carcinoma (AFP-PGC) and non-AFP-PGC with modified docetaxel-cisplatin-5-fluorouracil regimen. Median progression-free survival was 7.7 months (95% confidence interval [CI]: 5.7-9.7) for AFP-PGC and 7.1 months (95% CI: 6.6-7.6) for non-AFP-PGC patients ($p = 0.46$).

prevalence is reported to be higher in the USA compared with the Eastern countries (15% versus 1.3-6.3%, respectively) [17]. This might be related to ethnic variations in addition to the differences in techniques and cut-off values used in AFP measurement. The rate of AFP-PGC in our study was 20.1%, which is almost higher than the rate in the USA. However, it is difficult to estimate if this result reflects the actual rate of AFP-PGC in our country, for several reasons. First, our study is retrospective with a small sample size, from a single institute. Second, most of our patients were male in both groups, and similarly is reported in the literature [18,19]. Third, the median age in our groups (54 and 57 years) was lower compared to that reported in the literature.

The expression of epithelial tumor markers, such as CEA or Ca 19-9, can be increased in epithelial tumors, but their sensitivity and specifity differ according to the histopathological subtypes. The specifity and sensitivity of these tumor markers are lower in gastric cancer [20,21]. On the other hand, AFP has a high sensitivity in hepatocellular carcinoma. In our study, AFP was significantly decreased after the third cycle of mDCF regimen in AFP-PGC group. Therefore, high basal AFP levels could be used as a prognostic factor of chemotherapy response in AFP-PGC.

In our study, the liver was the most common site of metastasis in AFP-PGC group, furthermore, liver metastasis was more common in AFP-PGC compared to non-AFP-PGC group (70.6% versus 31.9%, respectively, $p < 0.001$). The rate of liver metastasis observed in this study was almost higher than the rate reported in the literature (14-75%) [22-24]. Chang et al. reported a 72% liver metastasis rate in AFP-PGC patients (n = 24) [25]. However, the underlying molecular mechanisms of the higher rate of liver metastasis in AFP-PGC are still not clear.

In TAX 325 trial, docetaxel and cisplatin plus 5-fluorouracil (DCF) regimen was found as an effective therapy in metastatic gastric cancer patients [26]. In this study, the overall disease control rate was 67% (CR - 2%, PR - 35%, SD - 30%). However, grade 3-4 adverse effects were reported in 69% of patients. Secondary G-CSF prophylaxis was used in patients with complicated neutropenia [26]. Since the original DCF regimen in TAX 325 trial showed high toxicity rates, several studies evaluated the efficacy of mDCF regimen with lower doses [14-16]. The authors concluded that the efficacy of mDCF regimen was similar to that of the standard DCF regimen, but with a lower toxicity rate. In addition, Keskin et al. demonstrated the overall disease control rate of 90% (CR - 2%, PR - 54%, SD - 34%). The authors reported grade 3-4 anemia in 11% of the patients and grade 3-4 nausea and vomiting in 15% [14]. In a retrospective study that compared mDCF with CFF (cisplatin, 5- fluorouracil, folinic acid), as first-line therapy, mDCF chemotherapy regimen resulted in a higher response rate with similar toxicity as CFF regimen [27]. In another study, mDCF and standard DCF regimens were shown to have similar response rates, but mDCF chemotherapy regimen demonstrated a significantly lower toxicity rate [28]. The disease control rates in our study were comparable to those reported in the literature. In our study, the overall disease control rates were 79.6% (PR - 44.1%, SD - 35.3%) and 82.2% (CR - 3%, PR - 36.2%, SD - 43.0%) in AFP-PGC and non-AFP-PGC patients, respectively. In previous studies, median OS and PFS for mDCF regimen were reported as 8.7-10.7 months and 6.2-7.4 months, respectively [14-16,27,28]. In our study, the median OS and PFS were similar in both AFP-PGC and non-AFP-PGC group (11.3 months [95% CI: 8.0-14.7] and 11.4 months [95% CI: 10.2-12.5]; 7.7 months [95% CI: 5.7-9.7] and 7.1 months [95% CI: 6.6-7.6], respectively). The similar survival rates observed in both groups, indicate that mDCF regimen is effective in gastric cancer regardless of AFP secretion.

However, despite the OS and PFS rates were similar in both groups, in AFP-PGC group, none of the patients showed CR and the rate of patients with progressive disease was higher compared with the patients in non-AFP-PGC ($p = 0.74$). Although these results were not sufficient to demonstrate the aggressive behavior of AFP-PGC, some data indicate aggressive behavior of AFP-PGC compared with non-AFP-PGC. c-MET overexpression might also contribute to the aggressive behavior of AFP-PGC [29]. Hence, c-MET inhibitors could lead to better response rates in the patients with c-MET overexpression, however, prospective clinical trials are required in this area.

The small number of patients from a single institute, without the evaluation of immunohistochemical staining for AFP, is the major limitation of our retrospective study.

CONCLUSION

mDCF regimen is well-tolerated in both AFP-PGC and non-AFP-PGC patients. AFP might be used as a tumor marker in AFP-PGC patients. In addition, monitoring AFP level might contribute to the response evaluation in AFP-PGC. However, prospective randomized clinical trials are required to verify the clinical significance of AFP as a tumor marker in AFP-PGC.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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