

Decline of serum CA724 as a probable predictive factor for tumor response during chemotherapy of advanced gastric carcinoma

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Objective: To evaluate the predictive value of decline in the serum level of carbohydrate antigen 724 (CA724) on tumor response during the chemotherapy in patients with advanced gastric carcinoma (GC).

Methods: The serum CA724 level was determined by electrochemiluminescence immunoassay, while the objective response rate (ORR) was assessed according to response evaluation criteria in solid tumors (RECIST). The association of the changes of serum concentration of CA724 with ORR was analyzed.

Results: The ORR in CA724 (pretreatment serum level) high and low groups was 32.3% (20/62) and 52.8% (19/36), respectively (P=0.045). The relationship between the reduction of CA724 and the ORR was statistically significant (P=0.044). Receiver operating characteristic (ROC) curve established the best cutoff value of the decrease ratio of CA724 as 20.5%.

Conclusions: CA724 decline seems to indicate chemotherapy efficacy in patients with advanced GC, and an average drop of 20.5% in serum CA724 appears to predict the sensitivity to chemotherapy.

Keywords: Chemotherapy; predict; carbohydrate antigen 724 (CA724); advanced gastric carcinoma (GC)

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Introduction

Gastric carcinoma (GC) has emerged as a major public health problem and one of the most common malignancies in the world (1). Although its morbidity is sharply decreasing in the Western, GC keeps a high incidence in some eastern countries, such as Japan, Korea and China (2). Owing to its poor outcome, GC presents one of the great therapeutic challenges for oncologists (3). Palliative chemotherapy is the main option for GC patients with advanced stages to encourage survival outcomes and better quality of life (4,5). Therefore, it would be crucial to evaluate chemotherapy efficacy earlier and avoid ineffective treatment in time. However, imaging techniques used to estimate therapeutic effect are usually performed after various cycles of chemotherapy by macroscopic alterations of tumor diameter (6). Accordingly, to find an easier and cheaper tool to monitor the effects of chemotherapy would be extremely urgent.

Tumor biomarkers expressed in different biological tissues may reflect relative tumor burden and aggressive

biology (7). A meta-analysis showed that carbohydrate antigen 724 (CA724) was the most correlative serum tumor biomarker for the detection of GC in Chinese population (8). However, by now, there are few investigations focusing on CA724 for predicting the tumor response during chemotherapy. We examined the predictive value of serum CA724 for objective responses to the chemotherapy in patients with advanced GC.

Patients and methods

Patient selection

A group of 98 patients, at the Yancheng City No. 1 People's Hospital between October 2008 and October 2013, was included in the study meeting the following criteria: (I) pathologically confirmed and previously untreated adenocarcinoma arising from the stomach; (II) clinical tumor stage IIIc-IV, on the basis of the sixth edition of the American Joint Committee on Cancer (AJCC) (9); (III)

inoperable locally advanced or metastatic disease with measurable lesions by computed tomography (CT) scan; (IV) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; (V) an estimated life expectancy of at least 3 months; (VI) patients with adequate bone marrow, liver, heart, and renal functions; (VII) written informed consents were given before treatment; (VIII) the medical ethics committee of the Yancheng City No. 1 People's Hospital approved this study.

Treatment schedule

All patients were treated with an FLO regimen every 4 weeks of oxaliplatin 130 mg/m² on day 1 and leucovorin 50 mg/m² on days 1-5, each as an IV infusion followed by 5-fluorouracil 500 mg/m² as a 24-h continuous infusion on days 1-5. Treatment was repeated at most six cycles until disease progression, unacceptable toxicity, or withdrawal by the patient.

Evaluation of objective response

The clinical tumor response was assessed every two cycles of chemotherapy, using the RECIST criteria version 1.1 (10): complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The evaluation was performed 3 weeks after the treatment. Objective response rate (ORR) (%) = (CR + PR)/98 × 100%.

Serum assays for CA724

Venous blood samples were collected before chemotherapy and on the evaluation day after informed consent. Serum CA724 was measured by an electrochemiluminescence immunoassay on Roche Cobas e601 immunoassay analyzer (Roche Diagnostics, Germany). The recommended cutoff value of CA724 was less than 8.2 μ/mL. Levels below the cutoff value were defined as low while above the value as high. CA724 reduction ratio (%) = (1 - posttreatment level/pretreatment level) × 100%.

Statistical analysis

The chi-squared test and multivariate logistic regression analysis were used to assess the relationship between ORR and clinical variables. To obtain a nearly normal distribution in the raw data, raw CA724 serum values were transformed into a natural logarithm. CA724 values before chemotherapy were compared with those

after chemotherapy with the paired samples *t*-test. The independent sample *t*-test was applied to analyze the association of the decline ratio of CA724 with ORR. Receiver operating characteristic (ROC) curve was constructed to evaluate the role of CA724 reduction in predicting response to therapy. *P* < 0.05 was considered as statistical significance. Statistical analyses were conducted by Stata version 12.0.

Results

A total of 98 pathologically proven advanced GC patients were studied, and their characteristics are summarized in *Table 1*. There were 66 males and 32 females with a median age of 58 years (range, 35-70 years). The ORR was 39.80% with 2 CRs, 37 PRs, 39 SDs and 20 PDs. That was highly associated with the serum CA724 levels before chemotherapy; the difference in the ORR between CA724 high and low groups was significant (*P* = 0.045). In addition, the ORR was also correlated with histologic grade (*P* = 0.027) and distant metastasis (*P* = 0.017). *Table 2* indicates that by multivariate logistic regression analysis, the ORR was significantly associated with the pretreatment CA724 levels (OR = 1.037; *P* = 0.002; 95% CI, 1.013-1.061). There was also a marked association of the ORR with histologic grade (*P* = 0.024) and distant metastasis (*P* = 0.028).

At the beginning of chemotherapy, 62 (63.27%) patients had serum CA724 levels above the cutoff limit, with a median value of 25.51 μ/mL (range, 0.10-75.00 μ/mL). After 2-6 cycles of chemotherapy, the overall median value dropped to 18.56 μ/mL (range, 0.08-124.01 μ/mL). *Table 3* shows that the serum levels in different response groups declined significantly compared with baseline levels (*P* = 0.000, and *P* = 0.007, respectively; paired samples *t*-test). The mean reduction of CR + PR group and SD + PD group was 27.59% and -30.14%, respectively. There was a clear relationship between the reduction of CA724 and the ORR (*T* = 2.059, *P* = 0.044; independent sample *t*-test).

As shown in *Figure 1*, the decrease of CA724 in CR + PR group was related to the effectiveness of chemotherapy. The area under the ROC curve was 0.699 (*P* = 0.001, 95% CI, 0.594-0.805). The sensitivity (Se), specificity (Sp), positive (PPV), and negative predictive values (NPV) of CA724 are listed in *Table 4*. The optimum cutoff point for CA724 was achieved at a 20.5% reduction, with an Se of 69.2%, and an Sp of 62.7%. CA724 response was observed in 22 of 59 patients who had no objective response and in 27 of 39 responders ($\chi^2 = 9.583$, *P* = 0.002; chi-square test).

Table 1 Relationships of effectiveness of chemotherapy to clinicopathological factors and serum CA724 levels

Characteristics/markers	Effectiveness		χ^2	P
	CR + PR	SD + PD		
Sex			0.105	0.746
Male	27	39		
Female	12	20		
Age			1.674	0.196
≤60	20	38		
>60	19	21		
PS			0.909	0.340
>1	16	30		
≤1	23	29		
Regional lymph node metastasis			2.425	0.119
No	11	9		
Yes	28	50		
Distant metastasis			5.718	0.017
No	15	10		
Yes	24	49		
Histologic grade			7.236	0.027
Moderately differentiated	12	8		
Poorly differentiated	14	16		
Undifferentiated	13	35		
CA724 (μ/mL)			4.003	0.045
≤8.2	19	17		
>8.2	20	42		

CA724, carbohydrate antigen 724.

Table 2 Logistic regression analysis of the associations of serum CA724 levels with effectiveness of chemotherapy in the group of patients with ORR

Variables	OR	P	95% CI
CA724 (μ/mL)	1.037	0.002	1.013-1.061
Distant metastasis	3.553	0.028	1.145-11.025
Histologic grade	2.016	0.024	1.097-3.705

CA724, carbohydrate antigen 724; ORR, objective response rate.

Table 3 The comparison between the pre- and post-therapy levels of serum CA724 (paired sample *t*-test)

Effectiveness	Serum CA724		<i>t</i>	P
	Pre-therapy level	Post-therapy level		
CR + PR	2.026±1.483	1.693±1.392	14.549	0.000
SD + PD	3.187±0.982	3.006±0.943	2.818	0.007

CA724, carbohydrate antigen 724; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The strong association between ORR and CA724 response was confirmed by means of logistic analysis (OR =0.211; P=0.002; 95% CI, 0.150-0.621).

Discussion

Globally, GC is still the fourth most common cancer and the second leading cause of cancer-related mortality (11,12). Even though techniques of chemoradiotherapy, molecular target therapy and surgery are improving, the median survival for advanced GC remains at 8-10 months, with less than 10% 5-year survival (13). Anti-cancer drugs are highly toxic and expensive, and the ORR of first-line palliative chemotherapy has been reported to be 30-45% in advanced GC patients (14). Imaging techniques to estimate the therapeutic effect is limited by time, cost and clinical experience, which will fail to detect the presence of small hepatic and peritoneal metastases and vascular involvement (15). Thus, the development of simple and economical tools would be fairly desired in the field of treatment monitoring, estimating

prognosis and early prediction of response to therapy in order to optimize disease management on an individual basis. Tumor biomarkers are substances expressed in the process of tumorigenesis and progression that may indicate the presence of a neoplasm and/or reflect the relative malignancy burden and aggressive biology (16). Because of their easy and cost-effective measurement, tumor markers are expected to be potential factors for judging therapy efficacy and prognosis.

The European Society for Medical Oncology Clinical Recommendations and the National Comprehensive Cancer Network Clinical Practice for GC 2013 have not mentioned any tumor biomarker in the aspects of screening, diagnosis and follow-up monitoring (17,18). A wide range of serum biomarkers has been studied in connection with GC, in which more attention has been paid to CA724 (19,20). Aiming at Chinese population, a meta-analysis suggested that the single test of serum CA724 could do the best sensitivity and acceptable for the detection of GC (8). Higher serum concentrations of CA724 are positively related to TNM stage, recurrence, ascites, distant metastasis, risk of death and poor overall survival (21-23). Using logistic regression analysis, we found that ORR was clearly associated with the serum CA724 levels before chemotherapy, and the ORR in CA724 low group was significantly higher than that in CA724 high group. These facts may be explained by Yoon's findings that *in vitro* chemosensitivity of GC patients was negative correlated with pretreatment CA724 levels (24). Additionally, the ORR was found in association with histologic grade and distant metastasis, which was a reflection of prognosis (25).

The above results all put emphasis on the diagnostic and prognostic value of CA724. No data to date are available about the relationship between changes of serum CA724 level and tumor response during chemotherapy, which plays an important role for patients with advanced GC. Based on patients with unresectable locally advanced or metastatic

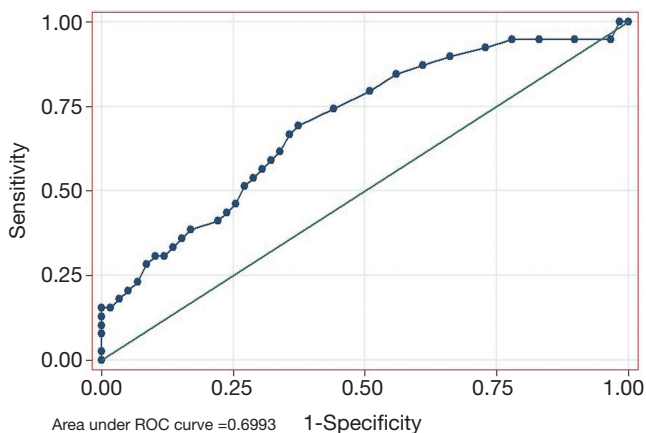


Figure 1 ROC curve for the chemotherapy effectiveness in relation to the decrease of CA724 in CR + PR group. ROC, receiver operating characteristic; CA724, carbohydrate antigen 724.

Decline ratio	Cutoff (%)	Se (%)	Sp (%)	PPV (%)	NPV (%)
CA724	19.5	74.4	55.9	52.7	76.7
	20.5	69.2	62.7	55.1	75.5
	21.5	66.7	64.4	55.3	74.5

Se, sensitivity; Sp, specificity; PPV, positive; NPV, negative predictive values; PPV, positive predictive values; CA724, carbohydrate antigen 724; GC, advanced gastric carcinoma.

GC, the present study of multiple analyses concentrated on the influence of changes in serum CA724 values on clinical benefits. The subjects underwent an FLO regimen and the ORR was 39.80%, in accordance with previous research (26). The serum CA724 concentrations in different response groups fell significantly compared with baseline levels. ROC analysis demonstrated that patients who experienced a drop of 20.5% in serum levels of CA724 gained a better tumor response than the others.

Conclusions

In conclusion, changes in serum CA724 level may help to predict the sensitivity to chemotherapy. It might be of clinical significance for oncologists to evaluate chemotherapy efficacy earlier and conveniently. In the future, we will enlarge sample size to minimize bias and further identify its value.

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