Original Article

Correlation between miR-138-5p expression and efficacy of platinum-based chemotherapy in advanced gastric cancer patients

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Background: We investigated the relationship between levels of microRNA (miR)-138-5p in plasma and tumor tissues from advanced gastric cancer patients, and the efficacy of first-line platinum-based chemotherapy.

Methods: MiR-138-5p expression was measured by qRT-PCR in cancerous tissues and plasma from 51 advanced gastric cancer patients, in paracancerous tissues and in plasma from healthy volunteers as control. All patients received first-line platinum-based chemotherapy. Correlations between miR-138-5p expression and the treatment efficacy, progression-free survival (PFS), and overall survival (OS) of first-line chemotherapy were evaluated.

Results: Significantly lower levels of miR-138-5p were detected in gastric cancer tissues compared with paracancerous tissues and in the plasma of patients compared with control subjects (both $P<0.05$). A positive correlation was detected between the treatment efficacy and miR-138-5p expression in both cancer tissues and plasma ($P<0.05$). Receiver-operating characteristic (ROC) curves were constructed to determine the optimal miR-138-5p cutoff value for predicting the efficacy of platinum-based chemotherapy. Patients with high miR-138-5p expression in either tissues (≥0.081) or plasma (≥0.047) had better treatment responses and longer PFS and OS than patients with low miR-138-5p expression ($P<0.05$), and multivariate analyses confirmed miR-138-5p expression as a promising prognostic biomarkers.

Conclusions: Our study suggested that miR-138-5p expression in cancer tissues or plasma could be a useful predictive biomarker for the efficacy of platinum-based chemotherapy and prognoses in advanced gastric cancer patients.

Keywords: Biomarker; chemotherapy; gastric cancer; miR-138-5p; platinum

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Introduction

Gastric cancer is one of the most common malignancies worldwide. In China, which has the highest morbidity rate from gastric cancer, the disease is the second most common malignancy in males, the third most common in females, and the second most lethal cancer overall (1). Most early-stage gastric cancer patients experience few symptoms, thus distant metastases are already present in about a third of patients at diagnosis (1). Palliative chemotherapies are the main treatment for advanced gastric cancer, but the prognosis remains dire. The standard first-line platinum-based chemotherapy consists of platinum and 5-fluorouracil (5-FU) (2); however, primary and secondary resistances limit the effective rate of platinum-based therapies to less than 50% (2). Moreover, the drastic differences in patient survival following treatments with the same platinum-based regimen suggest that other factors, such as genetic mutations, may influence the response. Thus, there is an urgent need to find biomarkers that can predict the efficacy of platinum-based therapies and guide individualized treatments. Recent works have shown that microRNAs (miRNAs) are potential biomarkers to predict the efficacy of palliative chemotherapy for advanced gastric cancer.

MiRNAs are a class of single-stranded RNAs that are aberrantly expressed in various cancers. In some cancer types, miRNA expression is closely related to cytotoxic agents' treatment sensitivity (3). Yang *et al.* found that overexpression of miR-138-5p in a non-small cell lung cancer (NSCLC) line inhibited DNA damage repair after radiotherapy (4). Wang *et al.* have suggested that miR-138-5p expression was associated with cisplatin resistance in the NSCLC cell line A549/DDP, which played pivotal roles in nuclear excision repair (NER) and the DNA damage response (5). We previously showed that miR-138-5p regulated the sensitivity of gastric cancer cells to cisplatin, possibly by modulating the expression of DNA repair proteins ERCC1 and ERCC4 (6). However, as most studies have been conducted in cell lines, whether a correlation exists between the efficacy of platinum therapies and the expression of miR-138-5p in tumor tissues and plasma from gastric cancer patients hasn't been elucidated yet.

To address this, we measured miR-138-5p expression in tissues and plasma from advanced gastric cancer patients and examined its correlation with the efficacy of platinum-based chemotherapies. The findings will contribute to the formulation of individualized regimens for gastric cancer, especially the application of platinum-combined therapies.

Methods

Study participants

The study was approved by the research ethics committee of the First Affiliated Hospital of Anhui Medical University (reference number: Quick-PJ 2016-11-11), and all individuals provided written informed consent. We enrolled a total of 51 patients (32 men, 19 women) treated at the Department of Oncology at the First Affiliated Hospital of Anhui Medical University from December 2014 to December 2015.

The inclusion criteria were: (I) diagnosed with gastric cancer pathologically by gastroscope biopsy or surgery; willing to provide plasma specimens before and after chemotherapies; considered to be stage IV according to the American Joint Committee on Cancer's Cancer Staging Atlas, 7th edition; (II) not receive palliative radiotherapy or other irrelevant chemotherapies; (III) confirmed to have measurable tumor targets by imaging tests; (IV) Easter Cooperative Oncology Group (ECOG) scores ≤2; (V) no history of other malignancies; (VI) normal hemogram and electrocardiogram and able to tolerate chemotherapy; (VII) willing to receive at least 2 cycles of treatment and cooperate with follow-ups.

Samples of cancerous tissues and paracancerous tissues (2 cm away from the tumor edge) were obtained from 51 and 20 patients respectively, fixed in formalin, and embedded in paraffin. Plasma was prepared from peripheral blood samples collected from the 51 patients (pre-treatment) and 20 healthy volunteers.

Treatment regimens

All patients received the platinum-based chemotherapies. The regimens consisted of cisplatin [75 mg/m^2; intravenous (i.v.) on days 1–3 or 1–5] or oxaliplatin (130 mg/m^2; i.v. infusion over 2 h on day 1) plus capecitabine (1,000 mg/m^2; twice daily on days 1–14) or S-1 (40–60 mg based on body surface area; twice daily on days 1–14. <1.25 m^2 =40 mg; 1.25–1.5 m^2 =50 mg; >1.5 m^2 =60 mg). Paclitaxel (135 mg/m^2 on day 1) or docetaxel (75 mg/m^2 on day 1) were added based on actual circumstances. Each cycle was separated by a 3-week interval.

Evaluation of efficacy

Chemotherapeutic efficacy was evaluated after two treatment cycles according to the Response Evaluation Criteria

in Solid Tumors guidelines (RECIST version 1.1) (7) as four outcomes, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR: CR+PR) and disease control rate (DCR: CR + PR + SD) were also assessed. PFS was defined as the interval from the date of first-line treatment to documented progression or death from any cause. OS was defined as the interval from the first day of treatment to death.

RNA extraction

Total RNAs were isolated from tissue blocks with a mirVana PARIS kit (Thermo Fisher Scientific) according to the manufacturer's instructions, and its purity was measured using a NanoDrop 1000 spectrophotometer. Only samples with OD_{260}/OD_{280} ratios between 1.8 and 2.1 were acceptable. After extraction, RNA samples were stored at −80 ℃ until analyzed. Venous blood was collected with EDTA anticoagulant tubes. Only non-hemolytic specimens were acceptable. Blood samples were centrifuged at 820 ×g for 10 min at 4 °C, and the supernatant was transferred to an RNase-treated tube and re-centrifuged at 1,600 ×g for 10 min. The supernatant was transferred to another RNase-free tube, and total RNA was extracted with a mirVana PARIS kit (Ambion #1556) (Thermo Fisher Scientific) according to the manufacturer's instructions.

Reverse-transcription quantitative PCR (qRT-PCR)

qRT-PCR was performed using an EzOmics One-Step qPCR Kit (Biomics). U6 mRNA and miR-16 levels were measured as internal references for tissue- and plasma-derived RNA respectively. Reaction mixtures (total 25 μL) consisted of specific primer pairs for miR-138-5p, U6, or miR-16, 2× Master Mix, and RNase-free DEPC water. Reactions were performed in an Mx3000P qRT-PCR system using reverse transcription for 30 min at 42 ℃, pre-denaturation at 95 ℃ for 10 min, annealing for 30 s at 60 ℃, and extension for 30 s at 72 ℃. After 40 cycles, the fluorescence signal was measured at 72 ℃. Relative miR-138-5p levels were calculated using the $2^{-\Delta\Delta CT}$ method and were normalized by subtracting the Ct values for miR-16 or U6 from that of miR-138-5p.

Statistical analysis

SPSS19.0 software (SPSS Inc., Chicago, IL, USA) was applied to statistical analysis. The Mann-Whitney *U* test was used for assessing miR-138-5p expression in gastric tissues and plasma. The ability of miR-138-5p expression to predict platinum efficacy was assessed by constructing receiver operator characteristic (ROC) curves. Survival was analyzed by the Kaplan-Meier method and log-rank test. The correlation between miR-138-5p expression in gastric cancer tissues and plasma was evaluated by linear correlation analysis. Univariate and multivariate Cox regression analyses were used to examine whether miR-138-5p expression could predict patients survival. A value of $P<0.05$ was regarded as statistically significant.

Results

MiR-138-5p expression in advanced gastric cancer

MiR-138-5p expression was measured by qRT-PCR, whose level in gastric cancer tissues was significantly lower than in paracancerous tissues (mean ± SD: 0.087±0.038 and 0.126±0.022, respectively; $Z=4.30$, $P<0.01$), as shown in *Figure 1A*. Similarly, miR-138-5p expression was significantly lower in plasma of patients with advanced gastric cancer than in that of healthy volunteers (0.071±0.037 and 0.097±0.014, respectively; $Z=3.0$, $P<0.01$), as shown in *Figure 1B*.

A linear correlation analysis showed that miR-138-5p expression in cancer tissues and plasma were positively correlated (Pearson's correlation $r=0.899$, $P<0.05$; $r^2=0.808$, *Figure 1C*), suggesting that the miR-138-5p expression in patient's plasma could represent its counterpart in cancer tissues.

Correlation between miR-138-5p expression and clinicopathological features of gastric cancer

As shown in *Table 1*, the miR-138-5p expression in advanced gastric cancer tissues and plasma did not correlate with patients' sex, ECOG score, tumor location, tumor tissue differentiation, liver or peritoneal metastasis, number of metastatic organs. However, higher miR-138-5p expression in cancer tissues was more likely to occur in patients aged below 60 ($P=0.03$).

Correlation between miR-138-5p expression in cancer tissues and the efficacy of platinum-based chemotherapies

In all 51 advanced gastric cancer patients, among whom the first-line platinum-based chemotherapeutic treatment

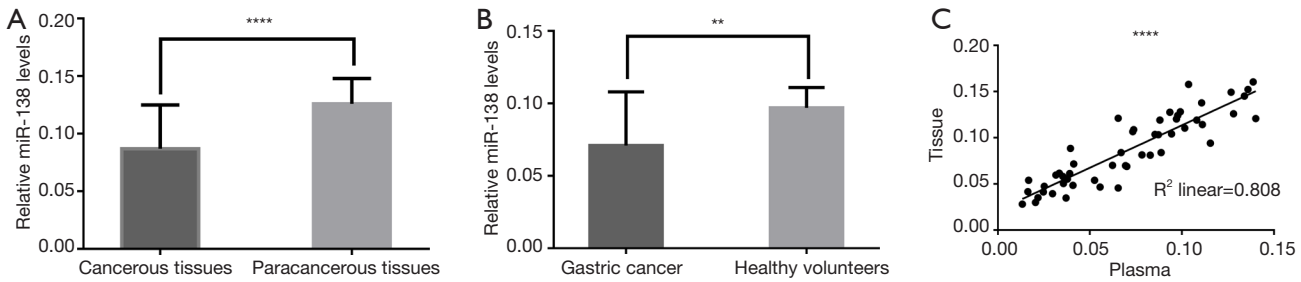

Figure 1 Relative expression of miR-138-5p. (A) MiR-138-5p expression in gastric cancer tissues (n=51) and paracancerous tissues (n=20). Data are presented as the mean ± SD normalized to tissue U6 mRNA levels in the same samples. ****, P<0.0001; (B) MiR-138-5p expression in plasma from gastric cancer patients (n=51) and healthy volunteers (n=20). Data are presented as the mean ± SD normalized to miR-16 levels in the same samples. **, P<0.01; (C) linear correlation analysis between tissue and plasma miR-138-5p expression in advanced gastric cancer patients. ****, P<0.0001.

Table 1 Association between miR-138-5p expression and clinicopathological factors

Characteristics	N	Percentage (%)	Plasma			Tissue		
			$2^{-\Delta\Delta CT}$ ($\bar{X}$±S)	t	P	$2^{-\Delta\Delta CT}$ ($\bar{X}$±S)	t	P
Gender				0.10	0.92		0.20	0.84
Male	32	62.7	0.072±0.038			0.088±0.040		
Female	19	37.3	0.071±0.036			0.086±0.036		
Age (years)				1.65	0.11		2.24	0.03
≥65	25	49.0	0.063±0.037			0.075±0.036		
<65	26	51.0	0.080±0.036			0.098±0.037		
ECOG (scores)				0.86	0.40		0.19	0.85
0–1	40	78.4	0.069±0.036			0.087±0.036		
2	11	21.6	0.080±0.044			0.089±0.048		
Differentiation				0.27	0.79		0.08	0.94
Poor	35	68.6	0.072±0.038			0.087±0.038		
Moderate and well	16	31.4	0.069±0.036			0.088±0.039		
Tumor location				0.26	0.80		0.11	0.91
Proximal and body	36	70.6	0.072±0.038			0.087±0.036		
Distal	15	29.4	0.069±0.037			0.088±0.045		
Liver metastasis				0.25	0.81		0.13	0.90
Present	21	41.2	0.073±0.036			0.086±0.037		
Absent	30	58.8	0.070±0.039			0.088±0.040		
Peritoneal metastasis				1.16	0.25		0.95	0.35
Present	6	11.8	0.055±0.034			0.073±0.031		
Absent	45	88.2	0.074±0.037			0.089±0.039		
Number of metastatic organs				1.12	0.27		1.12	0.27
1	22	43.1	0.065±0.039			0.080±0.038		
≥2	29	56.9	0.076±0.036			0.092±0.038		

ECOG, Easter Cooperative Oncology Group.

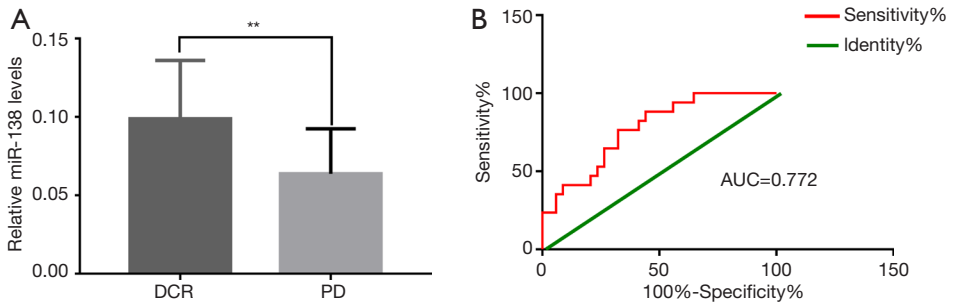

Figure 2 Relationship between tissue miR-138-5p expression and platinum-based chemotherapy efficacy. (A) Tissue miR-138-5p expression in DCR group and PD group. Data are presented as the mean ± SD. DCR (n=34), PD (n=17). **, P<0.01. (B) ROC curves to determine the specificity and sensitivity of tissue miR-138-5p expression level for predicting DCR to platinum-based chemotherapy. Red line: ROC curve; green line: diagonal line. DCR, disease control rate; PD, progressive disease; ROC, receiver-operating characteristic.

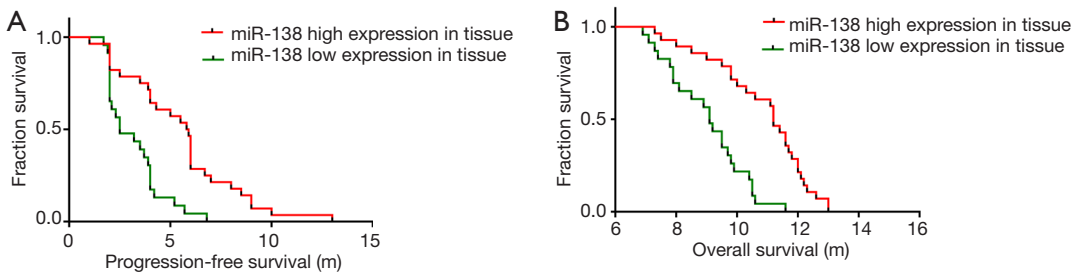

Figure 3 PFS (A) and OS (B) curves of patients stratified by high and low miR-138-5p expression levels in gastric cancer tissues. PFS, progression-free survival; OS, overall survival.

efficacy could be evaluated, 11 patients showed PR after treatment, whereas 23 patients exhibited SD, and 17 patients presented PD. ORR and DCR were 21.6% and 66.7%, respectively. The miR-138-5p expression in DCR group was higher than PD group (0.099±0.037 and 0.064±0.029, respectively; Z=−3.137, P<0.05, *Figure 2A*). We constructed ROC curve analysis to identify the optimal miR-138-5p expression cutoff value for DCR prediction. When the Youden index was at its maximum value, the area under the curve (AUC) was 0.772 (95% CI: 0.642–0.901) and the relative expression level of miR-138-5p was 0.081. The sensitivity and specificity for prediction of DCR were 67.65% and 76.47%, respectively (*Figure 2B*).

After 18 months of follow-up, all the 51 advanced gastric cancer patients died. The median PFS and OS were 4.0 months (95% CI: 3.76–4.3 months) and 9.9 months (95% CI: 9.2–10.6 months), respectively. Using the cutoff value of 0.081 as the discriminating point between high (n=28) and low (n=23) tissues miR-138-5p expression, the median PFS for the high and low groups were 5.8 months (95% CI: 5.1–6.5 months) and 2.5 months (95% CI: 1.1–3.9 months), respectively (log-rank, χ^2=15.94, P<0.05; *Figure 3A*). Similarly, the median OS of patients with high and low tissues miR-138-5p expression were 11.2 months (95% CI: 10.8–11.6 months) and 9.1 months (95% CI: 8.6–9.6 months) respectively (log-rank, χ^2=20.38, P<0.05; *Figure 3B*).

Correlation between miR-138-5p expression in plasma and the efficacy of platinum-based chemotherapies

The plasma miR-138-5p expression in DCR group was 0.083±0.036, which was significantly higher than that in PD group (0.048±0.029, Z=−3.107, P<0.01, *Figure 4A*). ROC curve analysis was also used to identify the optimal miR-138-5p expression cutoff value for DCR prediction here. When the Youden index reached its maximum, the AUC was 0.769 (95% CI: 0.636–0.902) and the plasma expression of miR-138-5p was 0.047. The sensitivity and specificity for prediction of DCR were 79.41% and 64.71% respectively (*Figure 4B*).

Using the cutoff value of 0.047 to distinguish between

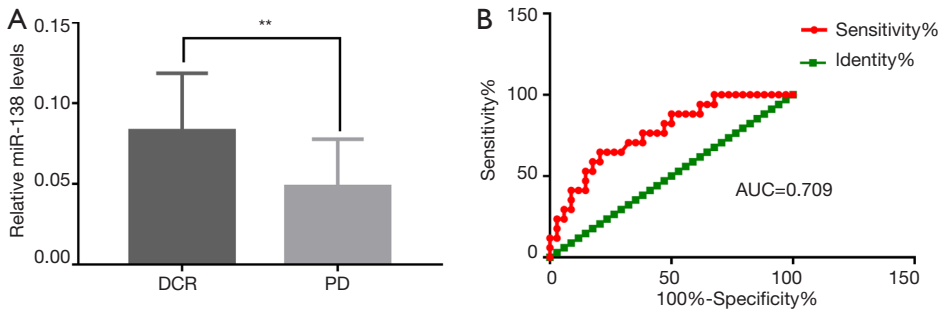

Figure 4 Relationship between plasma miR-138-5p expression and platinum-based chemotherapy efficacy. (A) Plasma miR-138-5p expression in DCR group and PD group. Data are presented as the mean ± SD. DCR (n=34), PD (n=17). **, P<0.01. (B) ROC curves to determine the specificity and sensitivity of plasma miR-138-5p expression level for predicting DCR to platinum-based chemotherapy. Red line: ROC curve; green line: diagonal line. DCR, disease control rate; PD, progressive disease; ROC, receiver-operating characteristic.

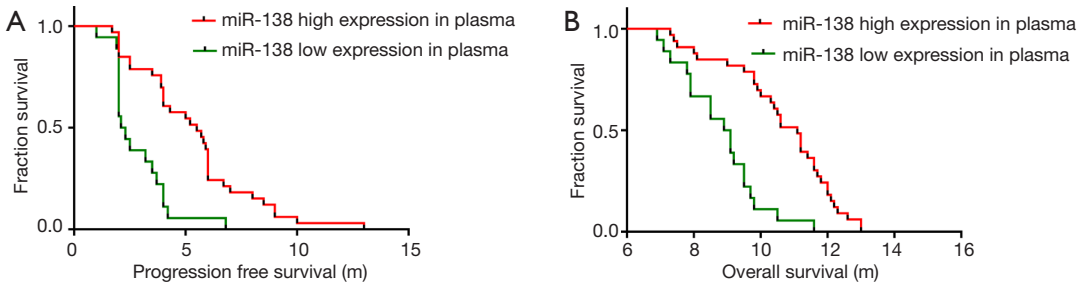

Figure 5 PFS (A) and OS (B) curves stratified by high and low miR-138-5p expression in plasma. PFS, progression-free survival; OS, overall survival.

high and low plasma miR-138-5p expression, patients in the high (n=33) and low (n=18) expression groups had median PFS of 5.5 months (95% CI: 3.8–7.2 months) and 2.1 months (95% CI: 1.5–2.7 months), respectively (log-rank, χ^2=16.48, P<0.05; *Figure 5A*). The corresponding median OS were 11.1 months (95% CI: 10.4–11.8 months) and 8.9 months (95% CI: 8.1–9.7 months), respectively (log-rank test, χ^2=20.2, P<0.05; *Figure 5B*).

Furthermore, univariate cox and multivariate cox analysis revealed that the miR-138-5p expression in tissues and plasma were both independent predictive factor for PFS and OS in advanced gastric cancer patients (all P<0.05) (*Tables 2,3*).

Discussion

Our previous studies demonstrated that the expression of miR-138-5p was significantly lower in the cisplatin-resistant advanced gastric cancer cell line SGC-7901/DDP compared with the sensitive line SGC-7901. We also showed that miR-138-5p overexpression could partially reverse cisplatin resistance by negatively regulating ERCC1 and ERCC4 enzyme activity and inhibiting the NER pathway (6). The results above suggested that miR-138-5p might be a potential therapeutic target, a predictive biomarker for sensitivity to platinum-based therapies, and/or a guide for individualized treatment. However, few studies have examined the miR-138-5p expression in advanced gastric cancer tissues or plasma, or its relationship with the efficacy of platinum-based chemotherapies. Therefore, we collected cancer tissues and plasma from 51 patients with advanced gastric cancer to explore whether the miR-138-5p expression can predict therapeutic efficacy and patients' prognosis.

MiR-138-5p is considered to be an anti-oncogene in many type of cancer cells include NSCLC cell (8), cervical cancer cell (9), oral squamous cell carcinoma (10), gallbladder cancer cell (11) and pancreatic cancer cell (12) and etc. Most studies on the effects of miR-138-5p upon drug responses have suggested that it has chemosensitizing

Table 2 Univariate Cox analysis of progression free survival and overall survival for gastric cancer patients

Parameters	Categories	HR (95% CI)	P value
PFS			
Age	≥65 *vs.* <65	1.082 (0.598–1.958)	0.794
Gender	Male *vs.* female	1.093 (0.615–1.941)	0.763
Grade	G1–2 *vs.* G3	0.784 (0.423–1.453)	0.444
ECOG	0–1 *vs.* 2	1.543 (0.775–3.072)	0.234
Liver metastasis	Present *vs.* absent	1.289 (0.729–2.279)	0.380
Peritoneal metastasis	Present *vs.* absent	0.702 (0.295–1.669)	0.442
Location	Proximal and body *vs.* distal	0.772 (0.413–1.443)	0.409
Number of metastatic organs	1 *vs.* ≥2	0.764 (0.426–1.369)	0.366
Chemotherapy regimens	Two drugs *vs.* three drugs	1.458 (0.697–3.050)	0.335
Chemotherapy response	CR + PR *vs.* PD	0.011 (0.001–0.093)	<0.001
	SD *vs.* PD	0.015 (0.002–0.119)	<0.001
miR–138–5p level (tissue)	Low *vs.* high	0.279 (0.146–0.533)	<0.001
miR–138–5p level (plasma)	Low *vs.* high	0.190 (0.089–0.405)	<0.001
OS			
Age	≥65 *vs.* <65	0.875 (0.493–1.554)	0.649
Gender	Male *vs.* female	1.536 (0.855–2.761)	0.158
Grade	G1–2 *vs.* G3	0.868 (0.472–1.596)	0.651
ECOG	0–1 *vs.* 2	1.391 (0.703–2.752)	0.357
Liver metastasis	Present *vs.* absent	1.121 (0.637–1.972)	0.692
Peritoneal metastasis	Present *vs.* absent	0.865 (0.366–2.046)	0.865
Location	Proximal and body *vs.* distal	0.968 (0.525–1.784)	0.916
Number of metastatic organs	1 *vs.* ≥2	0.694 (0.384–1.253)	0.225
Chemotherapy regimens	Two drugs *vs.* three drugs	1.739 (0.814–3.714)	0.153
Chemotherapy response	CR + PR *vs.* PD	0.078 (0.031–0.200)	<0.001
	SD *vs.* PD	0.151 (0.070–0324.)	<0.001
miR–138–5p level (tissue)	Low *vs.* high	0.214 (0.108–0.421)	<0.001
miR–138–5p level (plasma)	Low *vs.* high	0.155 (0.071–0.337)	<0.001

PFS, progression-free survival; OS, overall survival; ECOG, Easter Cooperative Oncology Group; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

activity. Wang *et al.* reported that the miR-138-5p expression was correlated with and played a role in cisplatin sensitivity of A549/DDP by negatively regulating ERCC1 and DNA repair (5). Yang *et al.* confirmed that miR-138 can diminish DNA repair in tumors by directly acting on H2AX (4). In osteosarcoma cells, upregulation of miR-138 increased the expression of the apoptosis effector protein caspase-3, which targeted EZH2 and enhanced cisplatin sensitivity (13). Studies in NSCLC cells showed that miR-138-5p enhanced doxorubicin sensitivity by targeting E-cadherin and ZEB2, downregulating vimentin, and inhibiting epithelial to mesenchymal transition (14). Han

Table 3 Multivariate analysis of progression free survival and overall survival for gastric cancer patients

Parameters	Categories	Plasma		Tissue	
		HR (95% CI)	P value	HR (95% CI)	P value
PFS					
Chemotherapy response	CR + PR *vs.* PD	0.018 (0.002–0.162)	<0.001	0.017 (0.002–0.146)	<0.001
	SD *vs.* PD	0.019 (0.002–0.153)	<0.001	0.020 (0.003–0.164)	<0.001
miR–138-5p level (tissue)	High *vs.* low	0.439 (0.200–0.961)	0.039		
miR–138-5p level (plasma)	High *vs.* low			0.378 (0.160–0.889)	0.026
OS					
Chemotherapy response	CR + PR *vs.* PD	0.110 (0.039–0.312)	<0.001	0.119 (0.042–0.336)	<0.001
	SD *vs.* PD	0.150 (0.067–0.339)	<0.001	0.209 (0.092–0.477)	<0.001
miR-138-5p level (tissue)	High *vs.* low	0.275 (0.130–0.583)	0.001		
miR-138-5p level (plasma)	High *vs.* low			0.283 (0.119–0.672)	0.004

PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

et al. showed that elevated miR-138 expression enhanced the sensitivity of NSCLC cells to cisplatin via CCND3 (15). In the cervical cancer HeLa cell line, miR-138-5p enhanced its sensitivity to 5-FU and adriamycin by downregulating FAK expression (16). Nevertheless, little is known about the involvement of miR-138-5p in gastric cancer.

In this study, we found that miR-138-5p expression was significantly lower in cancer tissues and plasma than in paracancerous tissues and normal plasma. This result herein was consistent with the researches aforementioned, suggesting that miR-138-5p might act as an anti-oncogene and a reduction in its expression contributed to the development of gastric cancer. The miR-138-5p expression was positively linked with the efficacy, PFS, and OS of first-line platinum-based regimens, which was in parallel with our previous studies on the effects of miR-138-5p on SGC7901/DDP and SGC7901 cells (6). Meanwhile, a similar chemosensitizing activity, which was unveiled in previous studies on miR-138-5p, was also observed here.

Recent studies have revealed that miRNAs can be readily detected in plasma, and the level often corresponded with that in tumor tissues (17). Microarray and PCR analysis of plasma samples have identified six miRNAs (miR-1, miR-20a, miR-27a, miR-34, miR-378, and miR-423-5p) that could serve as diagnostic biomarkers for gastric cancer, with miR-378 being specific for early stages. Other studies have demonstrated that circulating miR-214, miR-122, and miR-192 are novel biomarkers for gastric cancer that indicated severer metastases (18,19). Also, circulating miR-200c could predict the sensitivity of esophageal cancer to neoadjuvant chemotherapies and act as a prognostic biomarker (20). Our study identified a positive relationship between the miR-138-5p levels in tumor and plasma (Pearson's correlation r=0.899, P<0.05), which was consistent with the study of Tsujiura *et al.* (17), confirming that the plasma miR-138-5p expression could perform as a surrogate for tumor tissue biopsy to predict platinum-based chemotherapies efficacy and avoid difficulties in clinical collection of tumor tissues.

Previous studies have indicated that in advanced gastric cancer, those who responded well to first-line chemotherapies survive longer. Therefore, it would be of great benefit to screen patients for platinum sensitivity before drafting the first-line treatment regimen. Here, we found that the DCR, PFS and OS of platinum-based chemotherapies were significantly better in patients with a tissue miR-138-5p expression higher than 0.081 and a plasma level above 0.047. Univariate and multivariate analysis confirmed the higher miR-138-5p expression was independently correlated with longer PFS and OS.

The ORR and DCR of our cohort of 51 patients were 21.6% and 66.7%, respectively, and the corresponding PFS and OS were 4.0 months (95% CI: 3.7–4.3 months) and 9.9 months (95% CI: 9.2–10.6 months) respectively. Overall, these findings agreed with the results of previous studies. In advanced gastric cancer patients, due to the short post-diagnosis lifetime, ineffective chemotherapy may increase

suffering and compromising life quality. Thus, miR-138-5p expression may be used to predict the efficacy of postoperative adjuvant chemotherapy to avoid ineffective attempts and prolong disease free survival.

Conclusions

In conclusion, miR-138-5p expression in both cancer tissues and plasma could be potential biomarkers for predicting platinum-based treatment efficacy and prognosis of advanced gastric cancer, therefore guiding individualized treatments in clinical practice. Study limitations included the small sample size, chemotherapy regimens included cisplatin and oxaliplatin, and the focus on a single miRNA. Future studies should investigate the potential interactions among different miRNAs. Validation of our findings in a large prospective randomized clinical trial and stratified analysis of cisplatin and oxaliplatin will help to elaborate individualized treatments for gastric cancer in the clinics.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.11.25). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the research ethics committee of the First Affiliated Hospital of Anhui Medical University (reference number: Quick-PJ 2016-11-11), and all individuals provided written informed consent.

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