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ORIGINAL ARTICLE

Clinical significance of miRNA - 106a in non-small cell lung cancer patients who received cisplatin combined with gemcitabine chemotherapy

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ABSTRACT

Objective: Research has demonstrated that microRNA (miR)-106a is related to cisplatin resistance. We investigated the expression of miR-106a in the serum of patients with non-small cell lung cancer (NSCLC) and their sensitivity to chemotherapy by cisplatin combined with gemcitabine.

Methods: Eighty-five NSCLC patients, who completed four cycles of gemcitabine and cisplatin chemotherapy, volunteered for this study and their serum samples were collected. Serum samples from 60 healthy subjects were used as controls. Real-time quantitative polymerase chain reaction (real-time qPCR) was used to quantify the level of miR-106a in the serum. Demographic and survival data of these patients were collected for the analysis.

Results: The expression of miR-106a in the serum of NSCLC patients was significantly higher than that of healthy subjects ($P < 0.001$). The expression of miR-106a was not correlated with patients' gender, age, tumor size, lymphatic metastasis, and pathological types; but was correlated with patients' tumor staging ($P = 0.003$). After chemotherapy, serum miR-106a expression decreased in patients. The decrease in miR-106a expression in the chemotherapy-sensitive group was much higher than that in the chemotherapy-resistant group. Survival analysis shows that NSCLC patients with high expression of miR-106a have a poorer prognosis. The overall survival of NSCLC patients in the chemotherapy-sensitive group was significantly higher than that in the chemotherapy-resistant group.

Conclusions: High expression of miR-106a may be involved in the development of NSCLC. MiR-106a has significance in the prognosis of NSCLC. The level of miR-106a in the serum can be a useful parameter in screening for drug resistance during cisplatin-based chemotherapy.

KEYWORDS MiRNA-106a; NSCLC; cisplatin; gemcitabine; chemotherapy resistant

Introduction

Lung cancer is one of the most common malignant tumors in the world. The two main types of lung cancer are small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for 80% to 85% of lung cancers[1,2]. Despite improved surgical techniques and imaging equipment, and rapid developments in radiotherapy and chemotherapy methods, the treatment efficiency in NSCLC patients is still unsatisfactory. This is mainly because the majority of NSCLC patients are diagnosed at an advanced stage because of various reasons[3,4]. Chemotherapy is the main treatment method for advanced lung cancer. Drug resistance has become a major obstacle to successful chemotherapy in patients with lung cancer. In addition to the effective development of drugs, finding ways to prevent or identify drug-resistant cancers is another effective way to improve the efficiency of chemotherapy[5,6].

MicroRNAs (miRNA) are non-encoding RNAs, about 22 nucleotides long. MiRNAs play an important role in the regulation of various functions of cells[7,8]. Many miRNAs are upregulated or downregulated in human tumors, and abnormal expression of miRNAs could promote or suppress the development of tumors by affecting the expression levels of target proteins[9,10]. If miRNAs act on target proteins that affect absorption, metabolism, and distribution of drugs, or affect a target receptor that has an effect on clinical efficacy,

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these miRNAs could significantly affect the efficacy of anti-tumor drugs. Recent research has demonstrated that miRNAs play an important role in the chemotherapy resistance of malignant tumors[11,12].

MiR-106a has been identified as an oncogene that promotes the occurrence and development of tumors, and was found to be upregulated in a variety of tumors, including esophageal carcinomas[13], gastric cancer[14], and colorectal cancer[15]. Studies have also reported that the expression of miR-106a was significantly increased in NSCLC patients[16,17]. Mo et al.[18] screened miRNAs associated with cisplatin resistance in NSCLC cell lines. Their results showed that the expression of miR-106a in the NSCLC cell line A549 was more than 4 times of that in the cisplatin-resistant cell line A549/DDP. Fan et al.[19] showed that the level of serum miR-106a decreased in patients with metastatic colorectal cancer after being treated by immune cell therapy and chemotherapy. Gemcitabine combined with cisplatin is commonly used in treating NSCLC patients. In this study, we investigated the expression of miR-106a in NSCLC patients receiving both gemcitabine and cisplatin treatment, and explored the relationship of miR-106a expression with survival and chemotherapy resistance among these patients.

Patients and methods

Subjects and sample collection

Blood samples were collected from NSCLC patients who volunteered for the study from April 2010 to April 2012. All patients were pathologically diagnosed with NSCLC. The study was approved by the ethics committee of Tianjin Medical University Cancer Institute and Hospital in 2010. The ethics committee approved sample collection, data retrieval, and subsequent follow-up of these patients. All patients in this study (or their legal representative) gave informed consent. In addition, serum samples from 60 healthy volunteers were collected for comparison.

Inclusion and exclusion criteria

From April 2010 to April 2012, NSCLC patients' complete medical case histories were collected retrospectively. NSCLC was confirmed in all patients by histological and/or cytological diagnosis. The recruited patients' were ≥ 18 years of age. These patients received gemcitabine combined with cisplatin treatment (except for surgery resection) and had not receive chemotherapy, radiotherapy, targeted therapy or other treatments such as traditional Chinese medicine. The exclusion criteria were as follows: Non-primary NSCLC patients, patients with small-cell lung cancer or lack of cytology or histopathology results, patients with poor compliance during follow up, or patients with incomplete data.

Treatment

All patients were treated with gemcitabine at a dose of 1250 mg/m^2 of body surface area, via 30-min IV infusions on days 1 and 8, and cisplatin at a dose of 75–80 mg/m^2 of body surface area, via 3- to 4-hour IV infusions on days 2, 3, and 4 of each 3-week cycle after the end of gemcitabine infusion. A total of four treatment cycles were performed.

Data collection

The demographic data of these patients including gender, age, smoking habits, dates of diagnosis, dates of death, clinical stages, and pathological types were recorded.

Sample collection

Serum of NSCLC patients was collected before and after chemotherapy. Five milliliters of peripheral venous blood were collected from each subject and rapidly added into sterile test tubes without ethylenediaminetetraacetic acid (EDTA). The tubes were incubated for 10 min at 37 °C and centrifuged at 820 × *g* for 10 min at 25 °C. The supernatant was transferred to a clean 1.5 mL centrifuge tube and centrifuged at 16,000 × *g* at 4 °C for 10 min. The total RNA was extracted using the RNA Isolation Kit (Vazyme Biotech, Nanjing, China) from 500 μL of the supernatant. The concentration of RNA was determined by measuring the absorbance at 260 nm (A260) in a spectrophotometer (Biotek, San Diego, USA).

Measurement of miR-106a expression

Real-time quantitative polymerase chain reaction (RT qPCR) was used to detect miR-106a levels. One hundred nanograms of RNA were reverse transcribed into cDNA by the ReverTra Ace qPCR RT Kit (Toyobo Inc, Japan). The U6 small nuclear RNA (U6 snRNA) was selected as the internal reference. The designed RT-primer for miR-106a is 5′-GTCGTATCCA GTGCAGGGTCCGAGGTATTCGCACTGGATACGACCTA CCT-3′, and the PCR primers for miR-106 are upstream primer: 5′-GCGGCGGAAAAGTGCTTACAGTG-3′, and downstream primer: 5′-ATCCAGTGCAGGGTCCGAGG-3′. The U6 snRNA RT-primer sequence is 5′-AACGCTTCAC

GAATTTGCGT-3′, and the PCR primers for the U6 snRNA are upstream primer: 5′-CTCGCTTCGGCAGCACA-3′, and downstream primer: 5′-AACGCTTCACGAATTTGCGT-3′. The 7500 Real-Time PCR System (Applied Biosystems, Foster, CA, USA) was used for RT-PCR with the following conditions: 95 °C for 3 min, 95 °C for 10 s, 60 °C for 30 s, for 40 cycles. The expression of target genes was calculated using the $2^{-\Delta\Delta Ct}$ method: $\Delta\Delta Ct = Ct_{miR\text{-}106a} - Ct_{U6}$. The $2^{-\Delta\Delta Ct}$ value represents the relative expression of the target gene in the NSCLC group as compared with the control group.

Follow up

Telephone follow-ups were performed to record the patient's living conditions. The survival time of the patients was counted from the diagnosis of lung cancer to the date of death or the last follow-up date. The follow-up ended on November 2016.

Outcome measures: According to the Response Evaluation Criteria in Solid Tumors (RECIST), NSCLC patients were divided into a chemotherapy resistant group and a chemotherapy sensitive group, 4 weeks after treatment. The response was categorized as complete response (CR) or partial response (PR) for the chemotherapy sensitive group, and stable disease (SD) or progressive disease (PD) for the chemotherapy resistance group based on the following criteria: CR, the lesions disappeared, the duration > 4 weeks; PR, the maximum diameter of the tumor was reduced > 30% in a duration of > 4 weeks; SD, the maximum diameter of the tumor was reduced < 30% or increased ≤ 20%; PD, the maximum diameter of the tumor increased > 20% or new lesions were discovered. In addition, the overall survival (OS) time of these patients was calculated. OS was defined as the time from administration of chemotherapy until the date of death or last follow-up date.

Statistical analysis

An analysis database was established using the SPSS 19.0 statistical software. The Chi-squared test was used for comparisons between NSCLC patients and healthy volunteers, and subgroup-patients before and after treatment. The Kaplan-Meier method was used to calculate the median survival time and draw survival curves. The log-rank test was used to test the survival differences between different factors. A Cox proportional hazards model was used for the predictor analysis of patient survival. Two-sided tests were adopted in all tests. $P < 0.05$ was considered statistically significant.

Results

Demographic data of recruited subjects

Eighty-five NSCLC patients with complete medical case histories were ultimately recruited. Sixty-two patients were male and 23 were female. The average age of these NSCLC patients was 59.38±9.08 years, and their ages ranged from 35 to 78 years with a median age of 61 years. The average age of healthy controls was 62.34±8.88 years. A comparison of demographic data (**Table 1**) showed that there were no statistical differences in age, gender distribution, and other demographic information.

Relative miR-106a expression before chemotherapy

The relative miR-106a expression in NSCLC patients before treatment (relative expression: 5.10 ±1.98) was significantly higher ($P < 0.001$) than in healthy controls (0.41 ±0.15). Further analysis showed that the relative expression of miR-106a (**Table 2**) had no correlation with gender, age (< 55 or ≥ 55 years), lymphatic metastasis, or pathological types in NSCLC patients, but was correlated with the differentiation degree and TNM stage of NSCLC patients. The lower the degree of differentiation, the higher the relative expression of

Table 1 Demographic data of NSCLC patients and healthy control

Item	NSCLC patients	Healthy control	*P*
Number	85	60	
Age (mean ±SD, years)	59.38±9.08	62.34 ±8.88	0.053
Gender			0.415
Male	62	40	
Female	23	20	
Smoking index			0.440
≥400	16	9	0.55
<400	69	51	
Hyperlipidemia patients	19	13	0.93
Alcohol user	9	6	0.91
Hypertension patients	8	9	0.304
CHD patients	4	6	0.22
Diabetic	3	4	0.39

Table 2 Expression of miR-106a in NSCLC patients

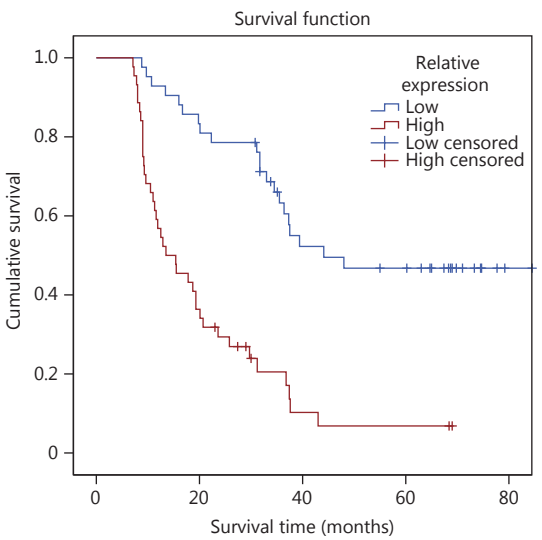
Item	*n* (%)	Relative miR-106a expression	*P*
Gender			0.57
Male	62	5.16±1.48	
Female	23	4.93±2.00	
Age (years)			0.31
<55	31	4.81±2.04	
≥55	54	5.26±1.93	
Tumor size (cm)			0.38
<3	35	4.87±2.15	
≥3	50	5.26±1.91	
Vascular invasion			0.83
No	34	4.996±1.97	
Yes	51	5.09±2.04	
Lymphatic metastasis			
No	53	4.89±1.98	0.18
Yes	32	5.44±1.44	
Differentiation degree			0.001
Well	10	2.95±0.93	
Moderate	30	5.02±1.59	
Poor	45	5.53±2.14	
TNM stages			0.003 (F: 6.282)
Stage Ⅱ	5	3.23±1.28	
Stage Ⅲ	43	4.62±2.05	
Stage Ⅳ	37	5.79±1.75	
Pathological type			0.14 (F: 2.01)
Adenocarcinoma	50	4.89±1.91	
Squamous	17	5.90± 2.08	
Others	18	4.69± 2.09	

miR-106a observed (2.95±0.93 in well-differentiated NSCLC *vs.* 5.53±2.14 in poorly differentiated NSCLC). Compared with patients in stage II and stage III, expression of miR-106a in stage IV patients was significantly higher (5.79 ±1.75 *vs.* 3.23 ±1.28 and 4.62 ±2.05, $P = 0.003$).

Survival of 85 NSCLC patients with high and low miR-106a expression

We compared the survival of the 85 NSCLC patients according to miR-106a expression; patients were divided into two groups according to the median value of miR-106a expression (4.83): a high miR-106a expression group and a low miR-106a expression group. Kaplan-Meier analysis (**Figure 1**) showed that the survival time of NSCLC patients with high miR-106a expression [21.39 ±2.63 (SEM) months, 95% CI: 16.23–26.54 months] were significantly shorter ($P = 0.000$) than that of patients with low miR-106a expression [54.51 ±4.67 (SEM) months, 95% CI: 45.37–63.66 months].

Relative miR-106a expression after chemotherapy: After four cycles of chemotherapy, relative miR-106a expression in NSCLC patients decreased significantly (**Figure 2A**). The relative expression of miR-106a decreased by 72% (average value of 1.41 ±1.04). According to the Response Evaluation Criteria in Solid Tumors (RECIST), the therapeutic effect of gemcitabine combined with cisplatin was divided into the chemotherapy sensitive group (CR+PR, n=35) and the chemotherapy resistant group (SD+PD, n=50). Results showed that there was no statistical difference between the average miR-106a expression in the chemotherapy resistant group and the chemotherapy sensitive group (5.06 ±1.75 *vs.* 5.02 ±2.35, $P = 0.08$). The expression of miR-106a decreased significantly ($P < 0.01$) in both groups after patients were treated by gemcitabine combined with cisplatin (1.57 ±1.01 in the chemotherapy resistant group *vs.* 1.17 ±1.05 in the chemotherapy sensitive group) when compared with the same group before treatment. Further analysis showed that the decrease in miR-106a expression in the chemotherapy sensitive group was significantly higher ($P = 0.011$) than in the chemotherapy resistant group after patients were treated



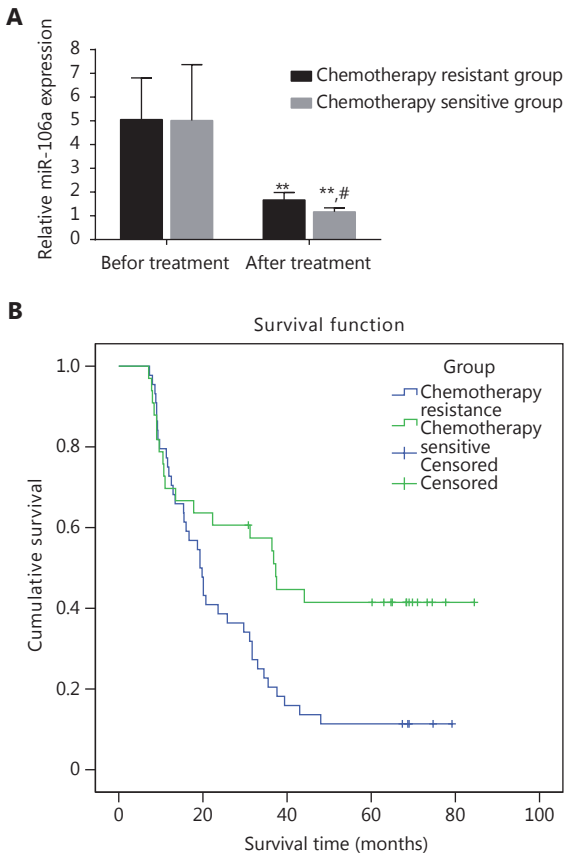


Figure 2 Comparison of miR-106a expression (A) and patients' survival according to their response to chemotherapy (sensitive or resistant) (B). **, $P<0.01$, compared with before treatment; #, $P<0.05$, compared with chemotherapy resistant group after chemotherapy treatment.

by gemcitabine combined with cisplatin. Survival analysis (**Figure 2B**) also showed that the survival of NSCLC patients in the chemotherapy sensitive group was significantly higher than in the chemotherapy resistant group [46.55 ±5.86 (SEM) months, 95% CI: 35.06–58.03 months *vs.* 27.15 ±3.21 (SEM) months, 95% CI: 20.85–33.45 months, $P = 0.022$].

Cox proportional hazards analysis

In this study, we analyzed the hazards factor for these NSCLC patients. Results showed that the relative expression of miR-106a ($P = 0.000$), lymphatic metastasis ($P = 0.017$), and the clinical stage IV ($P = 0.007$) were hazards factors affecting the survival of these NSCLC patients (**Table 3**), while age, gender, differentiation degree, pathological type, smoke index, and whether there was vascular invasion, had no effect on patients' survival.

Discussion

Lung cancer is a serious malignant tumor, threatening human health. There is no effective method for the clinical treatment of NSCLC. The abnormal expression of miRNAs is associated with many cancers. They play an important role in the occurrence and development of tumors and the aberrant expression of miRNAs is correlated with drug resistance. Mitchell et al.[20] demonstrated for the first time that miRNAs are stable in blood plasma and serum. Several more studies showed that there are specific circulating miRNAs expressed in the peripheral blood of patients with different tumors. The stability of miRNA in serum or plasma samples is not affected when left at room temperature for longer than 24 hours or when repeatedly frozen[21,22]. The expression profiles of miRNAs in different tumors are specific[23,24]. These characteristics indicate that the miRNAs in serum or plasma could serve as potential tumor markers. The detection of specifically expressed miRNAs in serum is a promising area of research in cancer biomarkers.

MiRNA-106a (miR-106a), a member of the miR-17 family, has been shown to be aberrantly regulated in a variety of tumors. Previous studies showed that miR-106a is aberrantly expressed in breast cancer, liver cancer, gastric cancer, etc. Our results suggest that miR-106a was highly expressed in the serum of NSCLC patients. The high expression of miR-106a was correlated with patients' clinical staging. Highly expressed miR-106a was also correlated with patients' prognoses, suggesting that miR-106a also plays an important role in NSCLC.

Chemotherapy is an important treatment method for advanced NSCLC. However, the long-term treatment efficacy of chemotherapy is restricted by drug resistance. The abnormal expression of a miRNA may lead to a loss or enhancement in the miRNA's function, thus affecting the expression levels of target proteins. If miRNAs act on target proteins affecting absorption, metabolism, and distribution of drugs, or affect a target receptor having an effect on clinical efficacy, the miRNAs could significantly affect the efficacy of anti-tumor drugs. Al-Khanbashi et al.[25] analyzed the miRNA profile of patients with locally advanced breast cancer (LABC) who received neo-adjuvant chemotherapy (NAC). MiRNA expression profiling of tumor versus normal tissues revealed more than 100 differentially expressed miRNAs. This indicated that variations in serum miRNA levels during NAC treatment might be therapeutically significant for predicting response and survival outcomes.

Mo et al.[18] examined miRNA expression differences by microarray in the cisplatin-resistant cell line A549/DDP and

Table 3 Multiple logistic regression analyzing factors affecting the overall survival of NSCLC patients

Item	B	S.E,	Wals	Sig.	Exp (B)	95% CI of EXP(B)	
Age	0.515	0.348	2.194	0.139	1.674	0.847	3.310
Gender	0.126	0.145	1.642	0.331	1.082	0.567	2.061
High miR-106a	2.73	0.57	22.81	0.000	15.28	4.99	46.77
Stage IV	–1.55	0.572	7.301	0.007	0.213	0.07	0.654
Vascular invasion	–0.22	0.636	0.001	0.972	0.706	0.415	1.199
Lymphatic metastasis	0.103	0.482	8.152	0.017	1.003	0.281	3.572
Differentiation degree	–0.643	0.534	1.446	0.229	0.536	0.185	1.499
Pathological type	–0.453	0.596	0.578	0.447	0.636	0.198	2.043
Smoke index	0.197	0.637	0.096	0.757	1.218	0.35	4.244
Constant	–0.264	1.319	0.04	0.842	0.768	--	--

the non-drug resistant cell line A549. Their results showed that the resistance of A549/DDP cells to cisplatin was 18 times that of A549 cells. Compared with A549 cells, the expression of miR-106a in A549/DDP cells was downregulated more than 4 times. While the results in many cancer patients are quite different, systematic research[26] on the diagnostic and prognostic values of miR-106a in patients with colorectal cancer (CRC), showed by pooled analysis that patients with higher expression of miR-106a in tissue had poor overall survival. Hou reported that miR-106a was significantly upregulated in gastric cancer patients' plasma samples[27]. Animal experiments also showed that the inhibition of miR-106a could inhibit tumor growth of ovarian cancers in mice[28]. Consistent with these studies, we found a higher expression of miR-106a in NSCLC patients compared to healthy controls, while gemcitabine combined with cisplatin decreased miR-106a expression. The chemotherapy-sensitive patients had lower miR-106a plasma expression compared to the chemotherapy resistant group in our study. Our research showed that miR-106a has the potential to be an auxiliary criterion of the curative effect of gemcitabine combined with cisplatin in NSCLC. The change in miR-106a expression level might be used as a reference to make necessary treatment adjustments for NSCLC patients, and finally to effectively prolong the survival time of patients. Of course, considering the small sample size of the study, these conclusions will need further follow-up studies for confirmation.

Chemotherapy based on platinum drugs is currently the standard treatment for advanced NSCLC. Cisplatin (DDP) is the most widely used clinical chemotherapy drug. The clinical effect of DDP is unanimously affirmed. The drug is safe, has low toxicity, good tolerance and other characteristics. DDP in the treatment of cancer is usually used as in combination with other drugs. Reports suggest that DDP combined with other anticancer drugs can achieve higher, effective survival rates in the treatment of cancers. It is reported that the upregulation of miR-106a promotes the survival of esophageal adenocarcinoma cells and confers resistance to DDP[29]. We found that the level of miR-106a is higher in DDP-resistant NSCLC patients than in DDP-sensitive patients. Several genes involved in cell proliferation and apoptosis are proposed to be regulated by miR-106a. Fang et al.[30] indicated that miR-106a confers DDP resistance by regulating the PTEN/Akt pathway in gastric cancer cells. Research by Rao showed that miR-106a targets Mcl-1 to suppress DDP resistance in ovarian cancer cells[31]. And Pan et al.[32] concluded that besides *FASTK* and *FAS*, six other genes (*SLC2A3*, *RBL2*, *IRS-2*, *CACUL1*, *FER1L4* and *E2F1*) can be targeted by miR-106a so as to regulate cell proliferation and apoptosis.

Our study indicates that miR-106a may play a key role in DDP-based chemotherapy resistance processes; due to the insufficient sample size, our study did not further examine the function and mechanism of miR-106a in the resistance to DDP combined with gemcitabine in NSCLC patients. We hope that further studies can elucidate the effects of miR-106a on the drug resistance to DDP-based chemotherapy in NSCLC. The upregulated expression of miR-106a in the plasma of NSCLC patients may have some clinical value in the diagnosis of NSCLC, but only using a miRNA as a tumor marker often lacks specificity. Combining many miRNAs and other types of tumor markers and establishing profiles of miRNAs will greatly improve the accuracy of diagnosis. We believe that with an in-depth study of plasma miRNAs in the diagnosis and treatment of tumors, the application will be more fruitful.

In conclusion, our study shows that miR-106a is

upregulated in the plasma of patients with NSCLC. Chemotherapy using gemcitabine combined with DDP can downregulate the expression of miR-106a. Compared to chemotherapy-resistant patients, the downregulation of miR-106a in chemotherapy-sensitive patients is more notable, which may provide some reference and a research base for the study of chemotherapy resistance and for the adjustment of DDP-based chemotherapy; but this conclusion still needs confirmation by further research.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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