Received: 27 September 2017 | Accepted: 31 October 2017

DOI: 10.1002/jcla.22363

RESEARCH ARTICLE

WILEY

Clinical value of peripheral blood microRNA detection in evaluation of SOX regimen as neoadjuvant chemotherapy for gastric cancer

Bibo Tan[1] | Yong Li[1] | Yan Di[2] | Liqiao Fan[1] | Qun Zhao[1] | Qingwei Liu[1] | Dong Wang[1] | Nan Jia[1]

[1]Department of General Surgery, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China

[2]Hebei Provincial Institute of Medical Science Information, Shijiazhuang, China

Correspondence
Yong Li, Department of General Surgery, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China.
Email: li_yong_hbth@126.com

Background: Neoadjuvant chemotherapy has been widely applied in treating advanced gastric cancer (GC). However, little research has been conducted on evaluating the effect of neoadjuvant chemotherapy. Purpose of this study was to evaluate the effect of SOX regimen as neoadjuvant chemotherapy by detecting some microRNAs.

Methods: Total 120 GC patients who had received neoadjuvant chemotherapy (SOX regimen) were recruited with 100 healthy participants as control contemporarily. Age and gender have no significant difference in both groups ($P > .05$). The effect of chemotherapy was evaluated by the results of CT scan and surgery. Also, adverse effects of chemotherapy were documented. Peripheral blood of GC patients was collected twice: one day before chemotherapy and surgery, respectively, whereas healthy controls' peripheral blood was collected once. Quantitative real-time PCR (qPCR) was utilized to detect expression of miR-145, miR-185, miR-381, and miR-195 of peripheral blood in both groups.

Results: One hundred and twenty patients with advanced GC completed a total of 386 cycles of neoadjuvant chemotherapy with effective rate at 84.17% (101 of 120). Expression of miR-145, miR-185, and miR-381 of patients with GC was lower than that in the control group before chemotherapy commence (all $P < .05$), while the expressions of miR-145 and miR-185 elevated noticeably in CG patients after neoadjuvant chemotherapy ($P < .05$). The differences in the expression of miR-145 and miR-185 in advanced GC patients with different chemotherapy outcomes were detected.

Conclusion: Patients with GC at advanced stages had aberrant miRs expressions. Detection of miR-145 and miR-185 expression may assist to predict effectiveness and adverse effects of SOX regimen as neoadjuvant chemotherapy.

KEYWORDS

advanced gastric cancer, biomarkers, microRNA, neoadjuvant chemotherapy, real-time PCR

1 | INTRODUCTION

GC is one of the most common malignancies with the second highest morbidity and mortality rate.[1] Early diagnosis is difficult because it is often asymptomatic or only moderate nonspecific symptoms are manifested at the early stage. Consequently, most patients suffer from the advanced stages of GC upon first diagnosis.[2-4] Treatments for advanced GC are mainly focused on surgical combined with adjuvant chemotherapy. However, surgical removal could not cure for a number of patients with late-stage GC. Therefore, to maximum

surgery outcome and improve prognosis, neoadjuvant chemotherapy has been adopted widely resulting in increased tumorectomy succeed and enhanced treatment outcomes.[5-8] However, the effectiveness of current chemotherapies in patients with GC remains unpredictable including neoadjuvant chemotherapy. If biomarkers are available for predicting outcomes and adverse effects of neoadjuvant chemotherapy, the treatment ratio for advanced GC may be able to improve. Therefore, new biomarker detection is of significance for clinical practice.

MicroRNAs are single-stranded RNA molecules with 18-25 nucleotides in length, having functions in regulating target post-transcriptional genes.[9-11] Recent findings show that microRNAs play a pivotal role in GC progress, and researches have revealed that in GC tissues or cells, miR-145, miR-185, miR-381, and miR-195 appear aberrant expression and also are involved in regulating GC cell proliferation, apoptosis, and metastasis.[12-15] However, little researches have been conducted to explore the expression of these microRNAs in peripheral blood of patients with GC and the association between expression of these microRNAs and neoadjuvant chemotherapy. This study aims to test the expression of miR-145, miR-381, miR-185, and miR-195 in peripheral blood of patients with GC and explore the possibility of their expression to be predictive markers for the outcome of neoadjuvant chemotherapy. A total of 120 patients with GC receiving SOX regimen as neoadjuvant chemotherapy were recruited, and the expression of miR-145, miR-381, miR-185, and miR-195 in their peripheral blood was investigated. In addition, these markers in predicting outcomes of neoadjuvant chemotherapy were further analyzed, and the results of this study may provide certain evidence to improve the GC treatment.

2 | MATERIALS AND METHODS

2.1 | Population study

A total of 120 patients with advanced GC received neoadjuvant chemotherapy in Fourth Hospital of Hebei Medical University were recruited between January 2015 and October 2016. The mean age of this group was (55.30 ± 7.11) years with males and females contributing 81 and 39, respectively. All patients met the criteria of recruit as following: (1) had received pathological endoscopic diagnosis of gastric adenocarcinoma at IIB-IIIC stage by CT scan staging according to the 7th edition of AJCC/UICC tumor staging system (2010); (2) were at their first visit without contraindications for surgery; (3) the informed consent in written was obtained for participation of SOX regimen. Criteria for exclusion were that GC patients: (1) with surgical history and diagnosed as recurrence, (2) combined with other malignancies, (3) had surgery contraindication, (4) who was not cooperative or refused to consent. Meanwhile, 100 healthy objectives as control were selected from physical examination department with no statistical significance in gender and age. Informed consent in written was obtained from all participants and approval from Ethics Committee of Fourth Hospital of Hebei Medical University was received.

2.2 | Neoadjuvant chemotherapy regimen and evaluation of its effectiveness

All participants received SOX chemotherapeutic regimen including Oxaliplatin and S-1 (Taiho Pharmaceutical Co.,Ltd). S-1 was taken orally on 40-60 mg/m^2 from the 1st to the 14th day, twice every day; with Oxaliplatin infused intravenously at 130 mg/m^2 on the first day. Followed by 1 -week break, one course of treatment was then completed. Each patient was scheduled with 2-4 periods of neoadjuvant chemotherapy. The chemotherapy was ceased immediately if patient suffered any serious adverse effect. CT scanning was applied both preoperatively and postoperatively. Participants were divided into four groups based on therapeutic efficacies which are rated as complete relief (CR, disappearance of primary lesion), partial relief (PR, >25% of primary lesion constriction), stable disease (SD, ≤25% of primary lesion constriction), and progressive disease (PD, >25% lesion enlargement). CR, PR and SD patients received surgical treatment after the chemotherapy, and the surgery anatomy was confirmed by CT results. Relevant adverse effects were recorded including myelosuppression or bone marrow suppression (anemia, leukopenia, and/or thrombocytopenia), and severe gastrointestinal reactions (required fluid resuscitation or even no tolerance to chemotherapy), or peripheral nervous damages. For bone marrow suppression, criteria included leukocyte reduction <4 × 10^9/L, neutrophil decrease <2 × 10^9/L, platelet reduction <50 × 10^9/L, or anemia (male HGB < 120 g/L, female HGB < 110 g/L). Severe gastrointestinal reaction is characterized by severe nausea and vomiting, requiring intravenous rehydration therapy. Criteria for peripheral neuropathy included significant sensory interference and abnormalities resulting from Oxaliplatin action.

2.3 | Sample collection

A total of 4 mL of fasting blood sample were collected each time per person for microRNA detection. Fasting venous blood was collected twice in participates of the case group with the first sample collected a day before chemotherapy and the second gathered 1 day before surgery. The blood samples were obtained from the control group only once. All of the blood samples were collected in anticoagulation tubes and stayed still for 30 minutes. After that, these samples were centrifuged for serum separation, and stored at −80°C.

2.4 | Quantitative PCR detection of miR-145, miR-185, miR-381, and miR-195 expression in serum

Total RNA was extracted from serum of blood samples, strictly following the manufacturer's instruction. All reagent kits targeting each microRNA were from GeneCopia, and U6 snRNA was utilized as internal reference gene. Reverse transcription reaction was carried out with 20- μL reaction system as following: Poly(A) reaction mixture 2 μL, 10 × RT Primer

TABLE 1 Comparison of miR-145, miR-185, miR-381, and miR-195 expression between patients with GC before chemotherapy and the control group

	miR-145	miR-185	miR-381	miR-195
GC group (120)	0.4136 ± 0.1606	0.2342 ± 0.1233	0.4856 ± 0.1947	0.2576 ± 0.1035
Control group (100)	0.5376 ± 0.1928	0.6375 ± 0.2903	0.7453 ± 0.2780	0.2411 ± 0.1097
t	−5.2048	−13.8024	−8.1203	1.1457
P	<.001	<.001	<.001	.2532

2 μL, 10 × RT Buffer 2 μL, Super Pure dNTPs 1 μL, RNasin(40U/μL) 1 μL, Quant RTase 0.5 μL, and RNase-Free ddH_2O 11.5 μL. The reaction system was placed at 37°C for 60 minutes after centrifugation, then stored at −20°C for PCR reaction. PCR procedures were performed with cycling parameters including 5-min denaturation at 95°C,followed by 95°C, 20 seconds of 60°C, 20 seconds of 72°C, and 20 seconds of 78°C, for 40 cycles. Fluorescent signal from each group was detected, using $2^{\Delta\Delta Ct}$ method to calculate the relative level of each microRNA.

2.5 | Statistical analysis

Research data statistically analyzed using Statistical Product and Service Solutions (SPSS) 18.0. MicroRNA's relative expressive level was expressed as mean ± SD ($\bar{x} \pm s$). Comparison of MicroRNA expression levels between case and control group was examined by independent samples *t* tests. In the case group, expression levels of microRNA before and after treatments were compared using paired sample *t* tests. One-way analysis of variance (ANOVA) was applied to examine differences in microRNA expression level between patients with different outcomes of treatment. Differences between any pair of means were detected using SNK test. Adverse events in relation to microRNA expression level were compared using group comparison *t* tests. Receiver operating characteristic (ROC) curve was applied for evaluation of the predictive value of microRNA expression level in diagnosis, outcome evaluation, and adverse effect prediction in gastric carcinoma. $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Efficacy of neoadjuvant chemotherapy

One hundred and twenty patients with GC in advanced stage had completed total 386 courses of neoadjuvant chemotherapy (all SOX regime) with mean (3.19 ± 0.98) courses for each patient. Evaluation was conducted in the end of each course of chemotherapy, and maximum of 4 neoadjuvant chemotherapy courses were received. Surgeries were performed on patients (CR + PR + SD) who achieved remission and stabilization, while patients with developing stage (PD) changed regimen to palliative chemotherapy. One hundred and twenty participants consisted of 6 CR patients (5.00%), 51 PR patients (42.50%), 44 patients with SD (36.67%), 19patients with PD (15.83%). The effective rate was 84.17% (101/120)(CR + PR + SD considered effective).

3.2 | Adverse response to neoadjuvant chemotherapy

Documentation focusing on major adverse chemotherapeutic effects mainly included bone marrow suppression, severe gastrointestinal reactions, and significant peripheral nerve damages. The criteria for adverse events are defined as following. In the case group, 31 patients had bone marrow suppression (25.83%), 18 suffered severe gastrointestinal reactions (15.00%), and peripheral nerve injury occurred in 38 case group members (31.67%).

3.3 | A comparison of miR-145, miR-185, miR-381, miR195 expression between patients with GC before neoadjuvant chemotherapy and the control group

Before neoadjuvant chemotherapy, lower expression levels of miR-145, miR-185, and miR-381 in serum of case group were detected compared with control group (all $P < .05$), while no statistical difference was shown between these two groups in the level of miR-195 ($P > .05$) (Table 1). ROC curve was used to illustrate the expression level of miR-145, miR-185, and miR-381 in the case group prior to neoadjuvant chemotherapy.

3.4 | Alteration in miR-145, miR-185, miR-381, and miR-195 serum expression levels of patients with GC after neoadjuvant chemotherapy

In the chemotherapy recipients, miR-145, and miR-185 levels elevated drastically, whereas changes in miR-381, and miR-195 levels before and after neoadjuvant chemotherapy were considered no statistical significance ($P > .05$) (Table 2).

3.5 | Association of serum levels of miR-145, miR-185, miR-381, and miR-195 in patients with GC before neoadjuvant chemotherapy and outcomes of the chemotherapy

Participants in case group were divided into 4 subgroups based on their responses to chemotherapy in terms of CR, PR, SD and PD, and the expression level of miR-145, miR-185, miR-381, and miR-195 was compared in these 4 subgroups. The results showed that a decrease in expression of miR-145 and miR-185 was found in 4 subgroups with a descending order from CR to PD ($P < .05$). miR-381 levels varied

TABLE 2 MiR-145, miR-185, miR-381, and miR-195 expression in patients with GC before and after chemotherapy

	miR-145	miR-185	miR-381	miR-195
Before therapy (120)	0.4136 ± 0.1606	0.2342 ± 0.1233	0.4856 ± 0.1947	0.2576 ± 0.1035
After therapy (120)	0.4806 ± 0.2473	0.3180 ± 0.1805	0.4975 ± 0.2695	0.2524 ± 0.1397
t	−7.8865	−4.1995	−0.3921	0.3276
P	<.001	<.001	.6954	.7435

TABLE 3 Serum expression of miR-145, miR-185, miR-381, and miR-195 in patients with GC before neoadjuvant chemotherapy with different treatment outcomes

	miR-145	miR-185	miR-381	miR-195
CR (6)	0.6655 ± 0.0732	0.4249 ± 0.0647	0.3817 ± 0.1067	0.2295 ± 0.1297
PR (51)	0.5097 ± 0.0671	0.2863 ± 0.1187	0.4627 ± 0.1882	0.2598 ± 0.1064
SD (44)	0.3350 ± 0.1656	0.1952 ± 0.0981	0.5566 ± 0.1889	0.2466 ± 0.1023
PD (19)	0.2579 ± 0.0547	0.1247 ± 0.032	0.4158 ± 0.2029	0.2863 ± 0.0908
F	41.2185	21.7502	3.8211	0.8014
P	<.001	<.001	.0118	.4937

TABLE 4 Adverse responses to chemotherapy and its association with the expression of miR-145, miR-185, miR-381, and miR-195 in patients with GC who underwent neoadjuvant chemotherapy

	miR-145	miR-185	miR-381	miR-195
Bone marrow suppression				
Yes (31)	0.2912 ± 0.0743	0.2288 ± 0.1014	0.4648 ± 0.1765	0.2499 ± 0.1043
No (89)	0.4562 ± 0.1609	0.2361 ± 0.1305	0.4929 ± 0.2011	0.2603 ± 0.1036
t	−5.4976	−0.2829	−0.6905	−0.4805
P	<.001	.7778	.4913	.6318
Gastrointestinal reaction				
Yes (18)	0.4515 ± 0.1610	0.2624 ± 0.0917	0.4586 ± 0.1741	0.2689 ± 0.0993
No (102)	0.4069 ± 0.1604	0.2293 ± 0.1278	0.4904 ± 0.1985	0.2556 ± 0.1045
t	1.0870	1.0505	−0.6373	0.5014
P	.2792	.2957	.5252	.6171
Peripheral nerve injury				
Yes (38)	0.4490 ± 0.1709	0.2515 ± 0.1015	0.4678 ± 0.1845	0.2528 ± 0.1019
No (82)	0.3971 ± 0.1539	0.2262 ± 0.1320	0.4939 ± 0.1998	0.2599 ± 0.1047
t	1.6589	1.0460	−0.6816	−0.3485
P	.0998	.2977	.4968	.7281

in each group ($P < .05$), but its level was not related to the outcome of neoadjuvant chemotherapy. miR-195 expression had no difference statistically in these groups ($P > .05$) (Table 3).

3.6 | Association of serum levels of miR-145, miR-185, miR-381, and miR-195 before chemotherapy with their related adverse events in GC

Results indicate that patients with bone marrow suppression had lower miR-145 expression compared with those without ($P < .05$), but this tendency of expression was absent in other microRNAs. The results also detected the expressions of these 4 microRNAs were not related to peripheral neuropathy ($P > .05$) (Table 4).

4 | DISCUSSION

In China, GC is one of the most common cancers and responds to a high mortality rate.[16] Despite numerous researches on it, there is still no highly effective treatment for GC.[17] Current treatments for GC are a combination of surgical, chemotherapy, radiation, target therapy and biotherapy, in which, surgery is particularly adopted as a main treatment.[18] However, surgery alone is not effective to treat patients with GC in advance stage. Many patients in advanced stage of CG suffered cancer recurrence soon after surgery. Therefore, neoadjuvant chemotherapy is recently widely utilized prior surgery to achieve the optimal outcome of CG treatment.[7,19,20] Neoadjuvant chemotherapy is a treatment applying on GC patients with advanced stage, and their

lesion is difficult to be removed surgically. The following treatment will be determined by the effects of neoadjuvant chemotherapy resulting in higher effective rate in surgical removal of GC lesion. SOX regimen is one of the common options for neoadjuvant chemotherapy with Oxaliplatin and S-1 as main targeting drugs accompanied with other types of drugs to subside the adverse effects with 3 weeks for one cycle.[21] In this study, most of the 120 neoadjuvant chemotherapy recipients had completed neoadjuvant chemotherapy as scheduled without any fatal side effects. This suggests that SOX regimen is safe for neoadjuvant chemotherapy. Our study finds that the percentage of patients responding to treatment (CR + PR + SD) reaches 84.17%, indicating that SOX regimen effectively suppressed cancer development. SOX regimen could be recommended for neoadjuvant therapy, and this result is consistent with other reports.[22] However, some patients with advanced CG still failed to respond to neoadjuvant chemotherapy and they lost the opportunity to receive further treatment. If biomarkers are available for evaluation, this type of patients would be benefited via choosing other suitable therapies, which might result in a better outcome. Therefore, our research investigated the value of microRNA in peripheral blood of patients with GC as potential biomarker to predict effects of SOX regimen.

MicroRNAs are a DNA-transcribed noncoding, and single-stranded RNAs, made of 18-24 nucleotides. The main function of microRNA is gene suppression which allows it to regulate its target genes and therefore to participate in biological regulation in cells.[23] It has been reported that miR-145, miR-185, and miR-381 were associated with GC.[12-15,24-27] It is reported that miR-145 could inhibit proliferation, migration, invasion, and cell cycle progression via targeting transcription factor Sp1 in gastric cancer cells.[28] Li Q et al[29] verified that miR-185 could increase the sensitivity of gastric cancer cells, and apoptosis repressor with caspase recruitment domain (ARC) is a direct target of miR-185. As for miR-381, Zhang M et al found that miR-381 could inhibit migration and invasion in human gastric carcinoma through downregulatedting SOX4, and targeting miR-381 may be a novel therapeutic option for the treatment of patients with GC.[30] However, little agreement is reached in relation to how these microRNAs express in the peripheral blood in patients with GC. This study reports that the expression of miR-145, miR-185, and miR-381 appeared altered in the peripheral blood in patients with GC. These three microRNAs can be potential novel marker s of GC examination, although more researches about their expression in the peripheral blood are still needed.

To understand the values and feasibility of these 4 microRNAs as biomarkers for neoadjuvant chemotherapy, this study examined the differences in the microRNA expression in the peripheral blood in neoadjuvant chemotherapy recipients before and after treatment. miR-145 and miR-185 were found increased levels in patients with GC after treatment. This result suggests that chemotherapy could influence miR-145 and miR185 levels. Furthermore, our study compared patients in PR, SD and PD groups in terms of therapeutic outcomes and microRNA expression in the peripheral blood. The result shows decreased expression of miR-145 and miR-185 in PR, SD, PD groups in a descending order. Accordingly, we conclude that a considerable decrease in miR-145 and miR185 in the peripheral blood may suggest unsatisfactory outcomes of SOX neoadjuvant chemotherapy. Another therapeutic option might be better. However, this conclusion requires further research conducted in multiple centers with a larger scale of samples to confirm.

We further analyzed the association of the 4 microRNAs with major adverse events in chemotherapy. Results show that the miR-145 expression was lower in patients with bone marrow suppression than those with none, while none of these mircroRNAs was correlated with gastrointestinal adverse reactions and peripheral nerve injuries. MiR-145 is suggested to be utilized to predict myelotoxicity before SOX neoadjuvant chemotherapy.

In sum, this study finds aberrant expression in advanced patients with GC their peripheral blood. Some microRNAs can assist in predicting outcomes and adverse events for neoadjuvant chemotherapy in GC. Further efforts should focus on elucidating the molecular mechanisms in a larger scale in associated with blood miR-145 and miR-185 their values of evaluating the effect of SOX regimen as chemotherapy for GC.

CONFLICT OF INTEREST

This study was approved by the ethics committee of the Fourth Hospital of Hebei Medical University. All patients and healthy controls in this study had written informed consent.

ORCID

Yong Li http://orcid.org/0000-0002-2592-5128

REFERENCES

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115-132.
2. Sun J, Wang D, Mei Y, et al. Value of the prognostic nutritional index in advanced gastric cancer treated with preoperative chemotherapy. *J Surg Res*. 2017;209:37-44.
3. Mashhadi MA, Sepehri Z, Bakhshipour AR, et al. Evaluation of Outcome and Tolerability of Combination Chemotherapy with Capecitabine and Oxaliplatin as First Line Therapy in Advanced Gastric Cancer. *Int J Hematol Oncol Stem Cell Res*. 2016;10:212-216.
4. Liu YY, Fang WL, Wang F, et al. Does a Higher Cutoff Value of Lymph Node Retrieval Substantially Improve Survival in Patients With Advanced Gastric Cancer?-Time to Embrace a New Digit. *Oncologist*. 2017;22:97-106.
5. Kim JS, Kang SH, Moon HS, et al. Clinical Outcome of Doublet and Triplet Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer. *Korean J Gastroenterol*. 2016;68:245-252.
6. West MA, Loughney L, Ambler G, et al. The effect of neoadjuvant chemotherapy and chemoradiotherapy on exercise capacity and outcome following upper gastrointestinal cancer surgery: an observational cohort study. *BMC Cancer*. 2016;16:710.
7. Qu J, Qu X. The predictors of response to neoadjuvant chemotherapy in patients with locally advanced gastric cancer. *Cancer Biomark*. 2016;17:49-54.
8. Ito S, Ito Y, Misawa K, Shimizu Y, Kinoshita T. Neoadjuvant chemotherapy followed by surgery in gastric cancer patients with

extensive lymph node metastasis. *World J Clin Oncol*. 2015;6:291-294.
9. Xu YF, Hannafon BN, Ding WQ. microRNA regulation of human pancreatic cancer stem cells. *Stem Cell Investig*. 2017;4:5.
10. Liu HT, Wang YW, Xing AY, et al. Prognostic Value of microRNA Signature in Patients with Gastric Cancers. *Sci Rep*. 2017;7:42806.
11. Zhang S, Ng MK. Gene-microRNA network module analysis for ovarian cancer. *BMC Syst Biol*. 2016;10:117.
12. Zhang Y, Wen X, Hu XL, et al. Downregulation of miR-145-5p correlates with poor prognosis in gastric cancer. *Eur Rev Med Pharmacol Sci*. 2016;20:3026-3030.
13. Tan Z, Jiang H, Wu Y, et al. miR-185 is an independent prognosis factor and suppresses tumor metastasis in gastric cancer. *Mol Cell Biochem*. 2014;386:223-231.
14. Cao Q, Liu F, Ji K, et al. MicroRNA-381 inhibits the metastasis of gastric cancer by targeting TMEM16A expression. *J Exp Clin Cancer Res*. 2017;36:29.
15. Deng H, Guo Y, Song H, et al. MicroRNA-195 and microRNA-378 mediate tumor growth suppression by epigenetical regulation in gastric cancer. *Gene*. 2013;518:351-359.
16. Chen W, Zheng R, Zeng H, Zhang S. The incidence and mortality of major cancers in China, 2012. *Chin J Cancer*. 2016;35:73.
17. Lazăr DC, Tăban S, Cornianu M, Faur A, Goldiş A. New advances in targeted gastric cancer treatment. *World J Gastroenterol*. 2016;22:6776-6799.
18. Choi YY, Noh SH, Cheong JH. Evolution of Gastric Cancer Treatment: From the Golden Age of Surgery to an Era of Precision Medicine. *Yonsei Med J*. 2015;56:1177-1185.
19. Yonemura Y, Ishibashi H, Hirano M, et al. Effects of Neoadjuvant Laparoscopic Hyperthermic Intraperitoneal Chemotherapy and Neoadjuvant Intraperitoneal/Systemic Chemotherapy on Peritoneal Metastases from Gastric Cancer. *Ann Surg Oncol*. 2017;24:478-485.
20. Li Z, Shan F, Wang Y, et al. Laparoscopic versus open distal gastrectomy for locally advanced gastric cancer after neoadjuvant chemotherapy: safety and short-term oncologic results. *Surg Endosc*. 2016;30:4265-4271.
21. Honma Y, Yamada Y, Terazawa T, et al. Feasibility of neoadjuvant S-1 and oxaliplatin followed by surgery for resectable advanced gastric adenocarcinoma. *Surg Today*. 2016;46:1076-1082.
22. Dong S, Yu JR, Zhang Q, Liu XS. Neoadjuvant chemotherapy in controlling lymph node metastasis for locally advanced gastric cancer in a Chinese population. *J Chemother*. 2016;28:59-64.
23. Masi LN, Serdan TD, Levada-Pires AC, et al. Regulation of Gene Expression by Exercise-Related Micrornas. *Cell Physiol Biochem*. 2016;39:2381-2397.
24. Li CY, Liang GY, Yao WZ, et al. Identification and functional characterization of microRNAs reveal a potential role in gastric cancer progression. *Clin Transl Oncol*. 2017;19:162-172.
25. Qiu F, Xiong JP, Deng J, Xiang XJ. TRIM29 functions as an oncogene in gastric cancer and is regulated by miR-185. *Int J Clin Exp Pathol*. 2015;8:5053-5061.
26. Li FQ, Xu B, Wu YJ, Yang ZL, Qian JJ. Differential microRNA expression in signet-ring cell carcinoma compared with tubular adenocarcinoma of human gastric cancer. *Genet Mol Res*. 2015;14:739-747.
27. Shen YH, Xie ZB, Yue AM, et al. Expression level of microRNA-195 in the serum of patients with gastric cancer and its relationship with the clinicopathological staging of the cancer. *Eur Rev Med Pharmacol Sci*. 2016;20:1283-1287.
28. Qiu T, Zhou X, Wang J, et al. MiR-145, miR-133a and miR-133b inhibit proliferation, migration, invasion and cell cycle progression via targeting transcription factor Sp1 in gastric cancer. *FEBS Lett*. 2014;588:1168-1177.
29. Qiu T, Zhou X, Wang J, et al. MicroRNA-185 regulates chemotherapeutic sensitivity in gastric cancer by targeting apoptosis repressor with caspase recruitment domain. *Cell Death Dis*. 2014;5:e1197.
30. Zhang M, Huang S, Long D. MiR-381 inhibits migration and invasion in human gastric carcinoma through downregulatedting SOX4. *Oncol Lett*. 2017;14:3760-3766.

How to cite this article: Tan B, Li Y, Di Y, et al. Clinical value of peripheral blood microRNA detection in evaluation of SOX regimen as neoadjuvant chemotherapy for gastric cancer. *J Clin Lab Anal*. 2018;32:e22363. https://doi.org/10.1002/jcla.22363