Int J Clin Exp Med 2020;13(4):2895-2901
www.ijcem.com /ISSN:1940-5901/IJCEM0107585

Original Article

Clinical value of PC combined with bevacizumab in patients with advanced non-small cell lung cancer and effects of serum miR-499

Zelan Xu, Junwei Du, Junhua Tang, Qinxing Xu, Xiaobo Ling, Yangfei Lu

Department of Respiratory Medicine, The First People's Hospital of Fuyang, Hangzhou, Zhejiang Province, China

Received January 8, 2020; Accepted February 11, 2020; Epub April 15, 2020; Published April 30, 2020

Abstract: Objective: This study aimed to investigate the clinical value of pemetrexed + cisplatin (PC) combined with bevacizumab (Bev) in patients with advanced non-small cell lung cancer (NSCLC) and effects of serum miR-499. Methods: Altogether 144 patients with NSCLC who received palliative chemotherapy in the first people's Hospital of Fuyang from December 2013 to July 2016 were selected as research subjects. Sixty-eight cases treated with PC were in a PC group, while the other 76 cases treated with Bev combined with PC (BPC) were in a BPC group. Their overall response rate (ORR), toxic and side effects, quality of life (QOL), 2-year progression-free survival (PFS), 2-year overall survival (OS), and serum miR-499 level were compared. Results: The ORR, 2-year OS, 2-year PFS, and improvement rate of QOL in the BPC group were better than those in the PC group. The number of cases of nausea and vomiting in the BPC group was higher than that in the PC group. Serum miR-499 level in the BPC group was higher than that in the PC group. The low expression of miR-499 was related to poor OS and PFS. The area under curve (AUC) of serum miR-499 for diagnosing the efficacy of palliative chemotherapy on NSCLC was 0.930. Conclusion: BPC has better clinical efficacy in patients with advanced NSCLC without increasing serious toxic and side effects, so this regimen can be popularized and applied in clinical practice. In addition, increasing miR-499 may be a strategy for treating NSCLC.

Keywords: PC, Bev, combination, advanced NSCLC, miR-499

Introduction

As a major cause of cancer deaths, lung cancer accounts for 10-13% of systemic malignant tumors, with non-small cell lung cancer (NSCLC) accounting for 80-85% of all lung cancer [1, 2]. The 5-year overall survival rate of the disease is currently <15%, because of its high recurrence, high metastasis, and limited therapeutic methods [3]. Since NSCLC has no specific clinical features in the early stage, most patients are already in the advanced stage when diagnosed and have lost their best treatment period [4]. For these patients, palliative chemotherapy is a major option whose purpose is mainly to prolong their life and improve their quality of life (QOL) [5]. At present, there are many chemotherapeutic drugs used in the clinical treatment of patients with advanced NSCLC, and combinations of different drugs have different effects. Therefore, the search for more effective drug combinations is a current hotspot.

The current standard regimen for treating advanced NSCLC is platinum-based drugs. However, this method only provides an objective remission rate of 30-40% and a median survival time of 8-11 months, which is unsatisfactory [6]. The development and application of targeted drugs provide new therapeutic directions for NSCLC, and targeted drugs combined with conventional chemotherapy have become a research hotspot at present. Bevacizumab (Bev), a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), can be used for treating a series of tumors including NSCLC [7]. Previous studies have found that Bev combined with platinum-based chemotherapy such as carboplatin/paclitaxel or cisplatin/gemcitabine (GC) provides greater benefits for patients with NSCLC [8, 9]. Pemetrexed + cisplatin (PC) is commonly used for treating advanced NSCLC, and PC + Bev (BPC) is assumed to improve the clinical efficacy on the disease. microRNAs (miRs) are

non-coding small RNAs whose abnormal expression or mutation is believed to be the cause of many human diseases [10]. As a member of miRs, miR-449 expression downregulates in NSCLC, which implies a poor prognosis [11].

Accordingly, it is speculated that BPC can improve the clinical efficacy against advanced NSCLC, which may be partially due to changes in miR-499 expression. In order to prove the correctness of the hypothesis, we designed the following research to find a more effective and safer therapeutic scheme for the disease.

Materials and methods

General information

This study has been approved by the medical ethics association of the First People's Hospital of Fuyang. The research objects were 144 patients with NSCLC who received palliative chemotherapy in the First People's Hospital of Fuyang from December 2013 to July 2016. Sixty-eight cases treated with PC were in the PC group, while the other 76 cases treated with BPC were in the BPC group. Inclusion criteria were as follows: patients aged 18-75 years; patients with life expectancy >12 weeks; patients with a Karnofsky Performance Scale (KPS) score ≥70%; patients with good organ function; patients confirmed with TNM stages (IIIb or IV) of non-squamous NSCLC by histology or cytology [12], those who were applicable to and had received palliative chemotherapy; patients with complete clinical data; patients without treatment within 30 days before enrollment; patients with lesions that could be measured. Exclusion criteria were as follows: patients with contraindications to the drugs used in this paper; patients with communication barriers; patients accompanied by other tumors; patients with infection. The patients and their guardians both signed the informed consent form.

Therapeutic methods

The therapeutic method in the BPC group was as follows: Bev (7.5 $mg \cdot kg^{-1}$) and pemetrexed (500 $mg \cdot m^{-2}$) were intravenously dripped on the 1st day; cisplatin (75 $mg \cdot m^{-2}$) was intravenously dripped on the 1st day or the 1st-3rd day. The therapeutic method in the PC group was as follows: pemetrexed (500 $mg \cdot m^{-2}$) and cisplatin (75 $mg \cdot m^{-2}$) were administrated using the same method as the BPC group. Three weeks were considered as 1 cycle, and patients in both groups were treated for 4 cycles.

Outcome measures

After 4 treatment cycles, the therapeutic effects on the PC and BPC groups were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) [13], including complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Overall response rate (ORR) = (CR + PR cases)/total number of cases × 100%.

Toxic and side effects during medication in the PC and BPC groups were recorded.

After 4 treatment cycles, KPS [14] was used to evaluate QOL in the PC and BPC groups. A score increasing by >10 points indicated improved; a score decreasing or increasing by ≤10 points indicated stable; a score decreasing by >10 points indicated worsen. Improvement rate = (improved + stable cases)/total number of cases × 100%.

The 2-year progression-free survival (PFS) and 2-year total survival (OS) in the PC and BPC groups were recorded. PFS was the time from the 1st day of treatment to lesion progression. OS was the time from the 1st day of treatment to patient death.

Changes in serum miR-499 expression were detected at 1 day before and 1 day after treatment. The detection method was as follows.

Detection of miR-499

A TRIzol reagent (Invitrogen, USA) was used to draw total RNA from the target cells, and its purity, concentration, and integrity were detected by an UV spectrophotometer and agarose gel electrophoresis. The TaqMan™ Reverse Transcription Reagents kit (Invitrogen, USA) was used for reverse transcription, with the specific steps strictly carried out according to the kit instruction. SYBR_Premix ExTaq II (Takara, China) and an ABI 7500 PCR instrument (Applied Biosystems, USA) were used for amplification. The system was as follows: 10 μL of SYBR Premix Ex Taq II (2X), 2 μL of cDNA, each 0.8 μL of upstream and downstream primers, and sterile purified water was finally added to supplement to 20 μL. Conditions for the amplification were as follows: predenaturation at 95°C for 30 s, denaturation at

Table 1. Comparison of clinical data [n (%)] (x ± sd)

Groups	PC group (n=68)	BPC group (n=76)	χ^2/F	P
Gender			0.766	0.382
Male	39 (57.35)	49 (64.47)		
Female	29 (42.65)	27 (35.53)		
Age (Years)			0.413	0.520
<60	24 (35.29)	23 (30.26)		
≥60	44 (64.71)	53 (69.74)		
History of smoking			1.483	0.223
Yes	28 (41.18)	39 (51.32)		
No	40 (58.82)	37 (48.68)		
Degree of differentiation			1.356	0.244
Highly/moderately	51 (75.00)	63 (82.89)		
Lowly	17 (25.00)	13 (17.11)		
TNM staging			0.125	0.724
IIIB	41 (60.29)	48 (63.16)		
IV	27 (39.71)	28 (36.84)		
Tumor diameter (cm)			0.323	0.570
≤5	29 (42.65)	36 (47.37)		
>5	39 (57.35)	40 (52.63)		
Lymph node metastasis			0.619	0.431
Yes	47 (69.12)	57 (75.00)		
No	21 (30.88)	19 (25.00)		

Table 2. Comparison of short-term efficacy [n (%)]

Groups	PC group (n=68)	BPC group (n=76)	χ^2	P
CR	9 (13.24)	18 (23.68)	2.572	0.109
PR	18 (26.47)	30 (39.47)	2.731	0.098
SD	29 (42.65)	21 (27.63)	3.570	0.059
PD	12 (17.65)	9 (11.84)	0.971	0.325
ORR	27 (39.71)	48 (60.53)	6.224	0.013

95°C for 5 s, and annealing and extension at 60°C for 30 s, for a total of 40 cycles. The data were analyzed using $2^{-\Delta\Delta ct}$ [15]. U6 was the internal reference of miR-499. Forward and reverse primer sequences of miR-499 were 5'-CACCCAAGTCTGGGGTGAAAGAGAAG-3' and 5'-GGTCATCAGCTTGTTGAGGTTC-3'. Primer sequences of U6 were 5'-GCTTCGGCAGCACATATACTAAAAT-3' and 5'-CGCTTCACGAATTTGCGTGTCAT-3'.

Data processing

SPSS20.0 was used to statistically analyze the collected data in this study. GraphPad 7 was used to plot the required figures. Chi-square test was used to compare the two groups in terms of count data such as clinical data, the number of cases of toxic and side effects, and short-term efficacy evaluation. Independent samples t test was used to compare the two groups in terms of measurement data such as miR-499 expression. The comparison between multiple groups was analyzed by one-way analysis of variance (ANOVA) and represented by F, and LSD-t test was used for post hoc pairwise comparison. The comparison of expression between multiple time points was analyzed by repeated measures ANOVA and represented by F, and Bonferroni was used for post hoc test. Kaplan-Meier (K-M) survival curve was plotted to show 2-year OS and RFS, and Log-rank test was used for analysis. Receiver operating curve (ROC) was plotted to evaluate the diagnostic value of serum miR-449 for the efficacy of palliative chemotherapy on advanced NSCLC. When P<0.05, there was a statistically significant difference.

Results

Comparison of clinical data

There were no statistically significant differences between the PC and BPC groups in terms of gender, age, history of smoking, degree of differentiation, TNM staging, tumor diameter, and lymph node metastasis (P<0.05). See **Table 1**.

Comparison of short-term efficacy

Patients in the PC and BPC groups have completed their respective treatments, as well as the tests and evaluations in this paper. After treatment, there were 9 cases (13.24%) of CR, 18 cases (26.47%) of PR, 29 cases (42.65%) of SD, and 12 cases (17.65%) of PD in the PC group, with an ORR of 39.71%. After treatment, there were 18 cases (23.68%) of CR, 30 cases (39.47%) of PR, 21 cases (27.63%) of SD, and 9 cases (11.84%) of PD in the BPC group, with an ORR of 60.53%. After treatment, ORR in the BPC group was higher than that in the PC group (P<0.05). See **Table 2**.

Comparison of toxic and side effects

The toxic and side effects during treatment were observed in the PC and BPC groups. There were no statistically significant differences

Table 3. Comparison of toxic and side effects [n (%)]

Groups	PC group (n=68)	BPC group (n=76)	χ^2	P
Anemia	7 (10.29)	5 (6.58)	0.648	0.421
Leukopenia	2 (2.94)	6 (7.89)	1.678	0.195
BMD	4 (5.88)	7 (9.21)	0.563	0.453
Hepatic function injury	1 (1.47)	2 (2.63)	0.237	0.626
Renal function injury	2 (2.94)	4 (5.26)	0.485	0.486
Nausea and vomiting	10 (14.71)	22 (28.95)	4.211	0.040
Hypertension	0	3 (3.95)	2.741	0.098

Table 4. Comparison of QOL

Groups	n	Improved	Stable	Worsen	Improvement rate (%)
PC group	68	12 (17.65)	27 (39.71)	29 (42.65)	39 (57.35)
BPC group	76	20 (26.32)	37 (48.68)	19 (25.00)	57 (75.00)
χ^2	-	-	-	-	5.029
P	-	-	-	-	0.025

between the two groups in major toxic and side effects such as anemia, leukopenia, bone marrow depression (BMD), hepatic function injury, renal function injury, and nausea and vomiting (P>0.05). The number of cases of nausea and vomiting in the BPC group was higher than that in the PC group (P<0.05). See **Table 3**.

Comparison of QOL

In the PC group, the QOL was improved in 12 cases (17.65%), stable in 27 cases (39.71%), and worsen in 29 cases (42.65%), with an improvement rate of 57.35%. In the BPC group, the QOL was improved in 20 cases (26.32%), stable in 37 cases (48.68%), and worsen in 19 cases (25.00%), with an improvement rate of 75.00%. The improvement rate of QOL in the BPC group was higher than that in the PC group (P<0.05). See **Table 4**.

Comparison of 2-year OS and PFS

Patients in the PC and BPC groups were followed up, without failure cases. The 2-year OS and PFS curves in two groups were plotted and analyzed by Log-rank test. Compared with those in the PC group, the 2-year OS prolonged (log-rank: P=0.015), and the 2-year PFS prolonged in the BPC group (log-rank: P=0.032). See **Figure 1**.

Changes in miR-499 level before and after treatment

PCR-qRT was used to detect changes in serum miR-499 levels in the PC and BPC groups before and after treatment. Before treatment, there was no statistically significant difference in serum miR-499 level between the two groups (P>0.05). After treatment, the level in the two groups increased, and the level in the BPC group was higher than that in the PC group (P<0.05). See **Figure 2**.

Analysis on prognostic value of miR-499

With the median expression level of serum miR-499 before treatment as the critical value, the patients were divided into a low expression group (n=83) and a high expression group (n=61). The 2-year OS and PFS curves in the two groups were plotted. According to the Log-rank test, compared with those in the low expression group, the 2-year OS prolonged (log-rank: P=0.002), and the 2-year PFS prolonged in the high expression group (log-rank: P=0.034). See **Figure 3**.

Diagnostic value of miR-449 for efficacy of palliative chemotherapy on advanced NSCLC

In results described above, patients with RR were taken as the RR group (n=75), while those with non-RR were taken as the non-RR group (n=69). Serum miR-499 level in the RR group was higher than that in the non-RR group (P<0.05). The ROC curve of the diagnostic value of serum miR-499 was plotted for the efficacy of palliative chemotherapy on advanced NSCLC. The area under curve (AUC) of serum miR-499 for the diagnosis was 0.930, the sensitivity was 86.67%, and the specificity was 91.30% (**Figure 4**).

Discussion

VEGF is a key factor required during tumor neovascularization and is highly expressed in lung cancer [16]. As the first drug approved by the Food and Drug Administration to inhibit tumor angiogenesis [17], Bev specifically binds to VEGF and blocks its biological activity, thus inhibiting tumor angiogenesis and treating the tumors [18]. According to previous studies, Bev combined with platinum-based chemotherapy

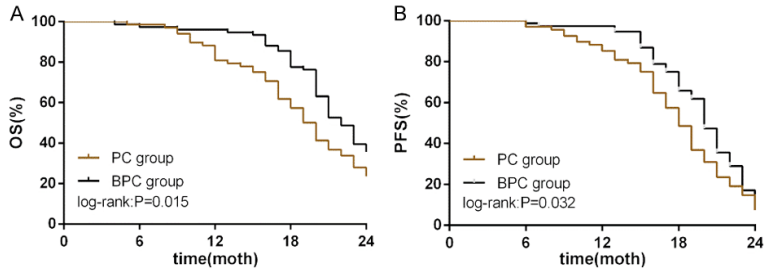

Figure 1. Comparison of 2-year OS and PFS. A. Compared with that in the PC group, the 2-year OS prolonged in the BPC group (log-rank: P=0.015). B. Compared with that in the PC group, the 2-year PFS prolonged in the BPC group (log-rank: P=0.032).

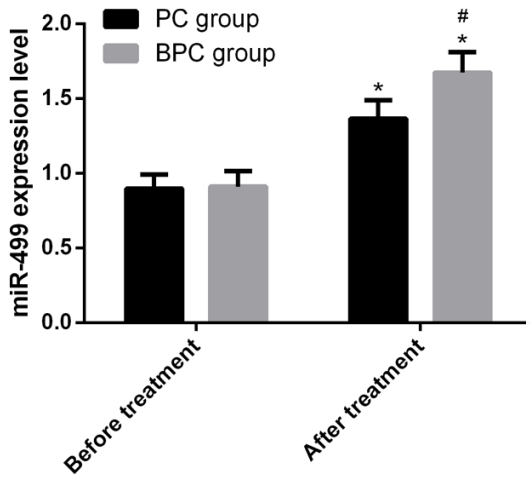

Figure 2. Changes in miR-499 level before and after treatment. According to PCR-qRT, after treatment, the level in the PC and BPC groups increased, and the level in the BPC group was higher than that in the PC group (P<0.05). Note: * indicates P<0.05 compared with that before treatment. # indicates P<0.05 compared with that in the PC group.

provides greater benefits for patients with NSCLC. A phase III study compared GC, GC + Bev (7.5 mg/kg), and GC + Bev (15 mg/kg) in the treatment of non-squamous NSCLC. The results showed that GC combined with Bev (7.5 or 15 mg/kg) could improve the patients' PFS and objective remission rate [19]. Another study compared the therapeutic value between Bev combined with GC and BPC in non-squamous NSCLC, and the results showed that patients treated with the former had better PFS and OS than those treated with the latter [20]. Therapeutic effects of PC combined with or without Bev on advanced NSCLC were compared in this study, and their short-term and long-term effects were observed. The ORR, 2-year OS, and 2-year PFS in the BPC group were better than those in the PC group. Subsequently, the occurrence of toxic and side effects during treatment were observed. The number of cases of nausea and vomiting in the BPC group was higher than that in the PC group. These findings indicate that BPC not only provides better clinical efficacy for the patients with advanced NSCLC, but also does not increase serious toxic and side effects. The patients' QOL was also assessed. The improvement rate of QOL in the BPC group was higher than that in the PC group. These findings are possibly explained by certain synergistic effects among the three drugs. Additionally, Bev reduces vascular permeability and tissue pressure in vivo, and increases concentrations of other drugs, thus improving its therapeutic effect [21].

As ubiquitous RNAs in human body, miRs are involved in various biological pathways, such as cell apoptosis, proliferation, differentiation, and metabolism [22]. miR-449 is a member of miRs that regulates the progression of various cancers. For example, it promotes colorectal cancer by targeting FOXO4 and PDCD4 [23], and promotes the progression of liver cancer through ets1 [24]. The down-regulation of its expression is associated with adverse results of NSCLC. Moreover, this miR plays an anticancer role through VAV3 [25]. These studies reveal that miR-499 plays a vital role in tumor progression. In this study, serum miR-499 level in the PC and BPC groups was higher after treatment than that before treatment, which indicates that reducing miR-499 level may be a way to treat NSCLC. The expression of serum miR-499 was also compared between the PC and BPC groups after treatment, and we found that the expression in the BPC group was higher than that in the PC group. This suggests that BPC can further decrease miR-449, thus inhibiting tumor growth, promoting cancer cell apoptosis, and reducing tumor malignancy. Finally, the clinical value of miR-499 in advanced NSCLC was explored. The low expression of miR-499 was related to poor OS and PFS, and miR-499 had the potential to diagnose the curative effect of palliative chemo-

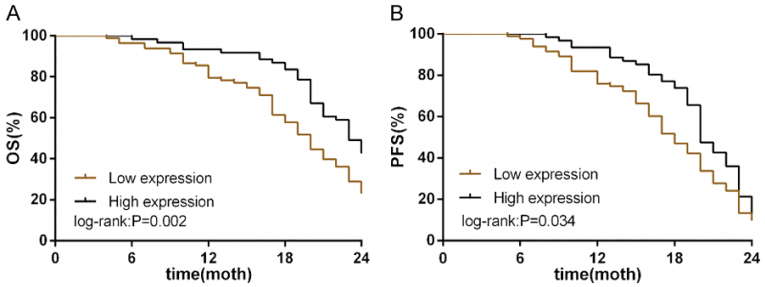

Figure 3. Correlation of miR-499 with OS and PFS. A. Compared with that in the low expression group, the 2-year OS prolonged in the high expression group (log-rank: P=0.002). B. Compared with that in the low expression group, the 2-year PFE prolonged in the high expression group (log-rank: P=0.034).

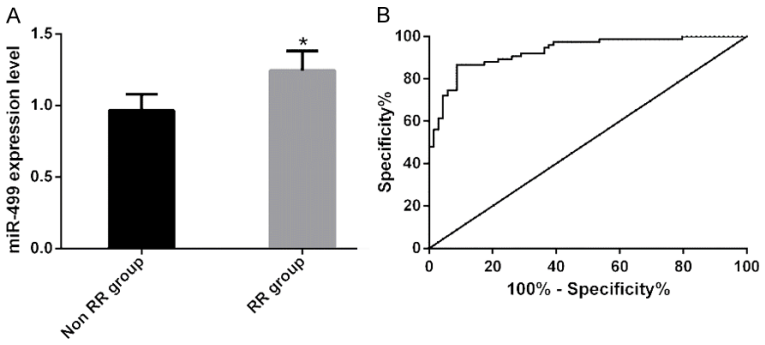

Figure 4. Diagnostic value of miR-449 for efficacy of palliative chemotherapy on advanced NSCLC. A. miR-499 expression in the RR group was higher than that in the non-RR group (P<0.05). B. The ROC curve. Note: * indicates P<0.05 compared with that in the non-RR group.

therapy on advanced NSCLC, with an AUC of 0.930. This demonstrates that miR-499 can be used as a potential marker for the poor prognosis of advanced NSCLC, and for diagnosing the curative effect of palliative chemotherapy on the disease.

It is found that BPC not only provides better clinical efficacy for patients with advanced NSCLC, but also does not increase serious toxic and side effects. However, there are some deficiencies in this paper. For instance, due to the limited time, this study has fewer research objects without longer follow-up. Additionally, this study was a clinical study, and cell experiments were not conducted to explore the correlation of miR-499 with NSCLC and the drugs used in this study. Therefore, it is hoped that the research objects will be enlarged and cell experiments will be carried out in future research to supplement the insufficiencies of this study.

In summary, BPC can provide better clinical efficacy for patients with advanced NSCLC without increasing serious toxic and side effects, so this regimen can be popularized and applied in clinical practice. In addition, increasing miR-499 may be a good strategy for the treatment of NSCLC.

Disclosure of conflict of interest

None.

Address correspondence to: Zelan Xu, Department of Respiratory Medicine, The First People's Hospital of Fuyang, No. 429 Beihuan Road, Fuchun Street, Fuyang District, Hangzhou, Zhejiang Province, China. E-mail: xuzhongcheng80@163.com

References

[1] Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, Zou W, Chen DS, Yi J, Sandler A and Rittmeyer A; POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016; 387: 1837-46.

[2] Masters GA, Johnson DH and Temin S. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Oncol Pract 2016; 12: 90-93.

[3] Wood SL, Pernemalm M, Crosbie PA and Whetton AD. Molecular histology of lung cancer: from targets to treatments. Cancer Treat Rev 2015; 41: 361-75.

[4] Wang X, Zhi X, Zhang Y, An G and Feng G. Role of plasma microRNAs in the early diagnosis of non-small-cell lung cancers: a case-control study. J Thorac Dis 2016; 8: 1645-52.

[5] Van Der Weijst L, Lievens Y, Schrauwen W and Surmont V. Health-related quality of life in advanced non-small cell lung cancer: a method-

ological appraisal based on a systematic literature review. Front Oncol 2019; 9: 715.
[6] Lee SY, Jung DK, Choi JE, Jin CC, Hong MJ, Do SK, Kang HG, Lee WK, Seok Y, Lee EB, Jeong JY, Shin KM, Yoo SS, Lee J, Cha SI, Kim CH and Park JY. PD-L1 polymorphism can predict clinical outcomes of non-small cell lung cancer patients treated with first-line paclitaxel-cisplatin chemotherapy. Sci Rep 2016; 6: 25952.
[7] Rosen LS, Jacobs IA and Burkes RL. Bevacizumab in colorectal cancer: current role in treatment and the potential of biosimilars. Target Oncol 2017; 12: 599-610.
[8] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R and Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355: 2542-50.
[9] Reck M, Von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N and Manegold C; BO17704 Study Group. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010; 21: 1804-9.
[10] Li G, Luo J, Xiao Q, Liang C and Ding P. Predicting microRNA-disease associations using label propagation based on linear neighborhood similarity. J Biomed Inform 2018; 82: 169-177.
[11] Li M, Zhang Q, Wu L, Jia C, Shi F, Li S, Peng A, Zhang G, Song X and Wang C. Serum miR-499 as a novel diagnostic and prognostic biomarker in non-small cell lung cancer. Oncol Rep 2014; 31: 1961-7.
[12] In H, Solsky I, Palis B, Langdon-Embry M, Ajani J and Sano T. Validation of the 8th edition of the AJCC TNM staging system for gastric cancer using the national cancer database. Ann Surg Oncol 2017; 24: 3683-3691.
[13] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.
[14] Chang JY, Verma V, Li M, Zhang W, Komaki R, Lu C, Allen PK, Liao Z, Welsh J, Lin SH, Gomez D, Jeter M, O'Reilly M, Zhu RX, Zhang X, Li H, Mohan R, Heymach JV, Vaporciyan AA, Hahn S and Cox JD. Proton beam radiotherapy and concurrent chemotherapy for unresectable stage III non-small cell lung cancer: final results of a phase 2 study. JAMA Oncol 2017; 3: e172032.
[15] Livak KJ and Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2-ΔΔCT method. Methods 2001; 25: 402-8.
[16] Hicklin DJ and Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005; 23: 1011-27.
[17] Khan P, Khan L and Mondal P. Cluster endophthalmitis following multiple intravitreal bevacizumab injections from a single use vial. Indian J Ophthalmol 2016; 64: 694-696.
[18] Randall LM and Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. Gynecol Oncol 2010; 117: 497-504.
[19] Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N and Manegold C. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. J Clin Oncol 2009; 27: 1227-34.
[20] Chang JW, Thongprasert S, Wright E, Tsang K, Kim HT, Ahn MJ, Kim JH, Kang JH, Kim SW and Walzer S. An indirect comparison of bevacizumab plus cisplatin-gemcitabine and cisplatin plus pemetrexed treatment for patients with advanced first-line non-squamous non-small cell lung cancer in East Asia. Asia Pac J Clin Oncol 2011; 7 Suppl 2: 13-21.
[21] Gonzalez J, Kumar AJ, Conrad CA and Levin VA. Effect of bevacizumab on radiation necrosis of the brain. Int J Radiat Oncol Biol Phys 2007; 67: 323-6.
[22] Lv C, Hao Y and Tu G. MicroRNA-21 promotes proliferation, invasion and suppresses apoptosis in human osteosarcoma line MG63 through PTEN/Akt pathway. Tumor Biol 2016; 37: 9333-42.
[23] Liu X, Zhang Z, Sun L, Chai N, Tang S, Jin J, Hu H, Nie Y, Wang X, Wu K, Jin H and Fan D. MicroRNA-499-5p promotes cellular invasion and tumor metastasis in colorectal cancer by targeting FOXO4 and PDCD4. Carcinogenesis 2011; 32: 1798-805.
[24] Wei W, Hu Z, Fu H, Tie Y, Zhang H, Wu Y and Zheng X. MicroRNA-1 and microRNA-499 downregulate the expression of the ets1 proto-oncogene in HepG2 cells. Oncol Rep 2012; 28: 701-6.
[25] Li M, Zhang S, Wu N, Wu L, Wang C and Lin Y. Overexpression of miR-499-5p inhibits non-small cell lung cancer proliferation and metastasis by targeting VAV3. Sci Rep 2016; 6: 23100.