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Review Article

Effects of bevacizumab combined with chemotherapy and radiotherapy on advanced non-small-cell lung cancer and on the expression of TPO and P-selectin

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Abstract: Objective: To investigate the effects of bevacizumab combined with chemotherapy and radiotherapy on advanced non-small-cell lung cancer (NSCLC) and on the expression of thrombopoietin (TPO) and P-selectin. Methods: Altogether 136 NSCLC patients admitted to Binzhou People's Hospital from February 2013 to May 2014 were collected, of which 74 patients were treated by bevacizumab combined with chemotherapy and radiotherapy as an observation group, and the rest 62 patients were treated with chemotherapy and radiotherapy alone as a control group. The efficacy, adverse reactions, and changes of TPO and P-selectin before and after treatment between the two groups were compared. Kaplan-Meier survival curves were employed to compare the 3-year survival of the two groups and 3-year survival of the high TPO and P-selectin expression groups and corresponding low expression groups, and the receiver operating characteristic (ROC) curves to analyze the value of TPO and P-selectin in predicting efficacy and survival. Results: The observation group obtained better efficacy than the control group, and the two groups had no difference in pernicious vomiting, myelosuppression, hypodynamia, rash, and liver function damage. After treatment, the observation group showed significantly lower TPO and P-selectin expression and better survival than the control group, and the survival of the low TPO and P-selectin expression groups was better than that of the high TPO and P-selectin expression groups. The area under the curve (AUC) of TPO and P-selectin in predicting efficacy was 0.830 and 0.776, respectively, and the AUC of them in predicting death was 0.872 and 0.844, respectively. Conclusion: Bevacizumab can enhance the efficacy of chemotherapy and radiotherapy on NSCLC and lower the expression of TPO and P-selectin, and TPO and P-selectin are expected to be predictive indicators of efficacy and prognosis for patients.

Keywords: Thrombopoietin, non-small-cell lung cancer, bevacizumab, chemotherapy, radiotherapy

Introduction

Lung cancer is the major cause of death for cancer among men in both developed and underdeveloped countries [1]. It is also the most common cancer in China and the major cause of death for cancer in China [2]. Non-small cell lung cancer (NSCLC) makes up about 80% of all lung cancers, covering large cell carcinoma, squamous cell carcinoma, and adenocarcinoma [3]. Lung cancer patients are easily misdiagnosed as other respiratory diseases, because there are no obvious characteristic symptoms in them in the early stage. Therefore, about 70% of the patients are already in the end stage at the time of diagnosis [4]. The patients at end stage often have already missed the best surgical resection time, so they are usually treated with radiotherapy and chemotherapy. Chemotherapy can mitigate NSCLC to a certain extent, but it is unable to radically cure advanced NSCLC, and it can only contribute to prolonging the treatment time of the patients as long as possible [5, 6]. In addition, chemotherapy can inhibit cancer cells during treatment, but it will also harm normal cells in the patients and lower the immunity of them [7]. Radiotherapy is an important local treatment method, but it only gives good result in small cell carcinoma, and cannot treat adenocarcinoma effectively. Furthermore, it is usually not used alone, but used with other treatment [8]. The 5-year survival rate (SR) of NSCLC patients is relatively low, generally about 15%, due

to the high deterioration degree, easy recurrence and easy metastasis [9].

Some studies revealed that platelet activation was a risk factor for some cardiovascular diseases and it could promote the development and metastasis of cancer [10]. Thrombopoietin (TPO) can promote stem cells to differentiate into megakaryocytes that can be converted into platelets. When platelets are activated, some factors will be rapidly expressed on the surface of some cells, and such kind of factors is P-selectin. Therefore, the activation of platelets can be understood by observing P-selectin [11]. P-selectin can lead to the formation of arterial thrombosis in cancer patients and worsen the prognosis of them [12]. A study by Grafetstätter et al. [13] pointed out that platelet activation and intensified coagulation state could promote the development of lung cancer, and P-selectin was strongly linked to lung cancer risk. Moreover, platelets also release some angiogenesis factors during activation to promote tumor development [14]. Bevacizumab is a targeted drug that inhibits tumor angiogenesis through targeted inhibition of vascular growth factors [15]. Tumor angiogenesis is associated with the proliferation and metastasis of the tumor, and bevacizumab inhibits tumor development by regulating tumor angiogenesis [16]. However, it is not clear whether bevacizumab combined with chemotherapy and radiotherapy affects the expression of TPO and P-selectin in advanced NSCLC patients.

Therefore, this study tried to explore the clinical efficacy of bevacizumab combined with chemotherapy and radiotherapy on advanced NSCLC and the changes of TPO and P-selectin expression during the treatment, so as to provide a basis and direction for clinical treatment of the cancer.

Materials and methods

Data about the patients

Altogether 136 patients treated in Binzhou People's Hospital from February 2013 to May 2014 were included, of which 74 patients were treated by bevacizumab combined with chemotherapy and radiotherapy as an observation group, and the rest 62 patients were intervened through chemotherapy and radiotherapy alone as a control group. The observation group included 43 males and 31 females, with an average age of 61.4±7.6 years, and the control group consisted of 33 males and 29 females, with a mean age of 62.2±6.8 years. The study was carried out under the permission of the Medical Ethics Committee of Binzhou People's Hospital, and each subject signed an informed consent form after understanding the study.

Inclusion and exclusion criteria

The inclusion criteria of the patients: Patients diagnosed with advanced NSCLC based on pathology according to the guidance released by the European Society for Medical Oncology in 2013 [17], patients who had not received radiotherapy and chemotherapy within one week before admission, patients not allergic to the therapeutic drugs, patients with expected survival time longer than one month, and patients with detailed clinical data and willing to cooperate for the treatment and follow-up.

The exclusion criteria: Patients with congenital immunodeficiency, severe infectious diseases or inflammatory disease, patients comorbid with other severe lung diseases, other malignant tumors, liver or kidney function obstacle, and pregnant or lactating women.

Reagents and instruments

TPO ELISA detection kit (Wuhan Elabscience Biotechnology Co., Ltd., E-EL-H1588c), P-selectin ELISA detection kit (Wuhan Elabscience Biotechnology Co., Ltd., E-EL-H0917c), bevacizumab (Roche Company, Switzerland), gemcitabine (Qilu Pharmaceutical (Hainan) Co., Ltd.), and cisplatin (Guizhou Hanfang Pharmaceutical Co., Ltd.).

Therapeutic regimen

Patients in the control group were intervened through radiotherapy and chemotherapy as follows: CT was adopted to locate the tumor position of the patients, and they were treated with three-dimensional radiotherapy at 2 Gy/time/day and 60 Gy/30 times for a total of 6 weeks, 5 times a week. Additionally, they were treated with gemcitabine at 1 g/m^2, one time a week, and also treated with cisplatin through intravenous drip at 80 mg/m^2, 3 times within one week. They rested for one month after every two cycles of chemotherapy, and they were

Table 1. Efficacy assessment

Efficacy classification	Assessment criteria
Complete remission (CR)	The tumor completely disappeared for more than 1 month.
Partial remission (PR)	The product of the maximum diameter and the maximum vertical diameter of the tumor decreased by 50% and other lesions did not increase for more than 1 month.
Stable disease (SD)	The product of the two diameters of the tumor decreased by no more than 50% or increased by no more than 25% for more than 1 month.
Progressive disease (PD)	The product of the two diameters of the tumor increased by more than 25%.
Objective mitigation (OR)	OR=CR + PR

treated for a total of 6 cycles. Patients in the observation group were additionally intervened with bevacizumab through intravenous drip at 7.5-12 mg/kg (once every three weeks) for 6 cycles in total, based on the intervention for the control group.

Efficacy

The efficacy of the two groups after treatment was analyzed according to the response evaluation criteria in solid tumors (RECIST) [18]. See **Table 1**.

Sample collection and ELISA

Venous blood (5 ml) was sampled from each patient under aseptic condition in the morning on the day when they were admitted to Binzhou People's Hospital and the next after treatment, respectively, and the blood was loaded into coagulation-promoting tubes. Subsequently, the blood was centrifuged at 3000 rpm for 10 min to separate the serum immediately after sampling. The separated serum was stored in a refrigerator at -80°C. The expression of TPO and P-selectin in the blood was determined using the enzyme-linked immuno-sorbent assay (ELISA). A blank well, a well for standards, and a well for samples to be determined were set, respectively. S0 standards with a concentration of 0 were added into the blank well, and 50 μL of standards with different concentrations were added into the well for standards. The well for samples to be determined was added with 10 μL of the samples and 40 μL of sample diluent. The black well was not added with sample diluent. Each well was added with 100 μL of horseradish peroxidase (HRP)-labeled detection antibody except the blank well. The reaction wells were blocked with a microplate sealer, and incubated in a water bath at 37°C for 65 min. The liquid in each well was discarded, and each well was patted to dry with an absorbent paper, filled with washing solution, and let to stand for 2 min. After the 2 min, the washing solution was shaken off, and each well was patted to dry with an absorbent paper again. After 6 repeats of the above steps, each well was added with 50 μL of substrate A and 50 μL of substrate B, and incubated at 37°C in the dark for 10 min. Each well was added with 50 μL of stop solution, and within 15 min after adding it, the optical density of each well was determined at 450 nm wavelength, on which the concentration of them was calculated.

Outcome measures

Primary outcome measures included the treatment efficacy in the two groups, TPO and P-selectin levels of the two groups before and after treatment, and the 3-year survival of the two groups.

Secondary outcome measures included the clinical efficacy in the two groups, the incidence of adverse reactions after treatment in the two groups, the TPO and P-selectin levels in patients with remission or non-remission, and the levels of the two factors in survival and dead patients.

Statistical analysis

In this study, the collected data were analyzed statistically using SPSS20.0 (Chicago SPSS Company, the United States), and visualized into figures using GraphPad Prism 7 (San Diego GraphPad Software Co., Ltd., the United States). The usage (%) of enumeration data was analyzed using the chi-square test, and expressed by X^2. Data distribution was analyzed using the Kolmogorov-Smirnov test, and measurement data were expressed by the mean ± standard deviation (Mean ± SD). All measure-

Table 2. Clinical data

Factor	The observation group (n=74)	The control group (n=62)	t/X^2	*P*-value
Sex			0.326	0.568
Male	43 (58.11)	33 (53.23)		
Female	31 (41.89)	29 (46.77)		
Age (Y)	61.4±7.6	62.2±6.8	0.641	0.523
BMI (kg/m^2)	21.35±1.37	21.73±1.53	1.527	0.129
Smoking history			0.018	0.893
Yes	16 (21.62)	14 (22.58)		
None	58 (78.38)	48 (77.42)		
History of alcoholism			0.252	0.616
Yes	13 (17.57)	13 (20.97)		
None	61 (82.43)	49 (79.03)		
Place of residence			0.028	0.867
Urban area	57 (77.03)	47 (75.81)		
Rural area	17 (22.97)	15 (24.19)		
Clinical stage			0.297	0.606
III b	47 (63.51)	42 (67.74)		
IV	27 (36.49)	20 (32.26)		
Pathological type			0.024	0.988
Squamous cell carcinoma	20 (27.03)	17 (27.42)		
Adenocarcinoma	45 (60.81)	37 (59.68)		
Others	9 (12.16)	8 (12.90)		
Lymph node metastasis			1.169	0.280
Yes	46 (62.16)	44 (70.97)		
None	28 (37.84)	18 (29.03)		
Differentiation			0.099	0.754
High differentiation	39 (52.70)	31 (50.00)		
Moderate and low differentiation	35 (47.30)	31 (50.00)		

ment data were in normal distribution, and inter-group comparison of the data was carried out using the independent-samples T test, and expressed by t. Receiver operating characteristic (ROC) curves were adopted to analyze the value of TPO and P-selectin in predicting efficacy and survival, and Kaplan-Meier (K-M) survival curves to draw the 3-year survival of the patients. The survival was analyzed using the Log-rank test. P<0.05 suggested a dramatic difference.

Results

Clinical data

Comparison of clinical data between the two groups revealed that there was no big difference between the two groups in terms of sex, age, body mass index (BMI), smoking history, alcoholism history, place of residence, clinical stage, pathological type, lymph node metastasis, and differentiation (all P>0.05). See **Table 2**.

Efficacy in the two groups

Comparison of efficacy between the two groups revealed that the odds ratio (OR) in the observation group was dramatically higher than that in the control group (P<0.05). See **Table 3**.

Adverse reactions during treatment

Comparison of adverse reactions between the two groups during treatment revealed that there was no big difference between them in pernicious vomiting, myelosuppression, hypodynamia, rash, and liver function damage (all P>0.05). See **Table 4**.

Table 3. Clinical efficacy

	The observation group (n=74)	The control group (n=62)	X^2	*P*-value
CR	19 (25.68)	11 (17.74)	1.235	0.266
PR	41 (55.41)	29 (46.77)	1.006	0.316
SD	11 (14.86)	16 (25.81)	2.538	0.111
PD	3 (4.05)	6 (9.68)	1.726	0.189
OR	60 (81.08)	40 (64.52)	4.756	0.029

Table 4. Adverse reactions

	The observation group (n=74)	The control group (n=62)	X^2	*P*-value
Pernicious vomiting	12 (16.22)	7 (11.29)	0.681	0.409
Myelosuppression	8 (10.81)	6 (9.68)	0.047	0.829
Hypodynamia	8 (10.81)	9 (14.52)	0.424	0.515
Rash	13 (17.57)	10 (16.13)	0.050	0.824
Liver function damage	4 (5.41)	4 (6.45)	0.067	0.796

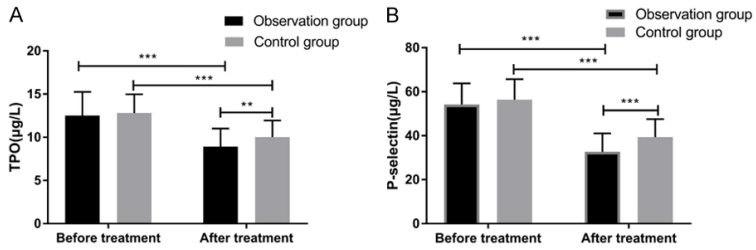

Figure 1. Changes in TPO and P-selectin levels before and after treatment. A. Before treatment, there was no difference between the two groups in TPO level (t=0.678, P=0.486), while after treatment, both groups showed a lower TPO level, and the observation group showed a significantly lower TPO level than the control group (t=3.152, P=0.002). B. Before treatment, there was no difference between the two groups in P-selectin level (t=1.343, P=0.181), while after treatment, both groups showed a lower P-selectin level, and the observation group showed a greatly lower P-selectin level than the control group (t=4.716, P=0.001). Note: ** means P<0.01 and *** means P<0.001.

TPO and P-selectin before and after treatment

In the study, we compared the changes in TPO and P-selectin levels before and after treatment in the two groups. It was found that before treatment, the observation group was not greatly different from the control group in TPO level (12.51±2.74 vs. 12.81±2.17, P> 0.05), while after treatment, both groups showed decreased TPO level (P<0.05), and the observation group showed significantly lower expression than the control group (8.93±2.08 vs. 10.02±1.92, P<0.05). In addition, it was also found that before treatment, the observation group was not much different from the control group in P-selectin level (54.16±9.63 vs. 56.36±9.37, P>0.05), while after treatment, both groups showed a decreased P-selectin level (P<0.05), and the observation group showed significantly lower expression of it than the control group (32.65±8.35 vs. 39.36± 8.16, P<0.05). See **Figure 1**.

Three-year survival

The observation group showed an overall survival rate (OSR) of 27.03%, with 20 patients survived and 54 patients died, while the control group showed an OSR of 17.74%, with 11 patients survived and 51 patients died. The survival curves of the patients showed that the survival of the observation group was much better than that of the control group (P<0.05). The patients were divided into high expression groups and corresponding low expression groups according to the median TPO and P-selectin expression before medication, respectively, in order to compare the survival of those groups. It was turned out that the SR of the high TPO expression group was dramatically lower than that of the low TPO expression group (P< 0.05), and the SR of the high P-selectin expression group was also dramatically lower than that of the low P-selectin expression group (P<0.05). See **Figure 2**.

ROC curves of TPO and P-selectin in predicting efficacy and survival

ROC curves were drawn according to the expression of TPO and P-selectin in patients with remission or non-remission in the observation group before treatment and the expression of them in survived patients and dead patients in the observation group before treatment. The curves showed that the expression of TPO and P-selectin in patients with remission was lo-

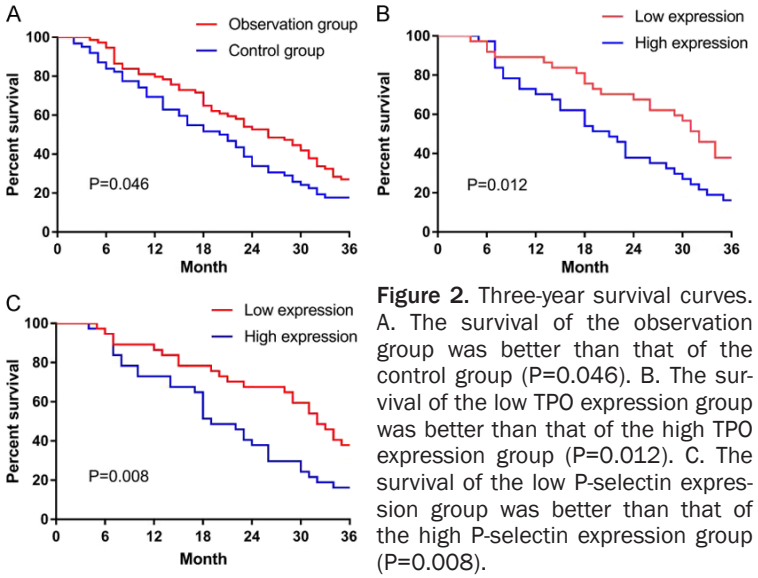

Figure 2. Three-year survival curves. A. The survival of the observation group was better than that of the control group (P=0.046). B. The survival of the low TPO expression group was better than that of the high TPO expression group (P=0.012). C. The survival of the low P-selectin expression group was better than that of the high P-selectin expression group (P=0.008).

wer than that in patients without remission (11.86±2.39 vs. 15.06±2.58 and 52.32±9.51 vs. 61.39±6.16), and the AUC of TPO and P-selectin was 0.830 and 0.776, respectively. The curves also showed that the expression of TPO and P-selectin in survived patients was lower than that in dead patients (9.73±1.52 vs. 13.54±2.35 and 46.08±8.01 vs. 58.74±8.42), and the AUC of TPO and P-selectin was 0.872 and 0.844, respectively. See **Table 5** and **Figure 3**.

Discussion

This study first compared the clinical efficacy of the two treatment methods. It was turned out that the observation group was not greatly different from the control group in CR, PR, SD, and PD, but the number of patients with CR in the observation group was greatly higher than that in the control group, which indicated that bevacizumab combined with chemotherapy and radiotherapy was superior to radiotherapy and chemotherapy alone with regard to efficacy and disease remission. Meantime, we also compared the adverse reactions during treatment between the two groups, finding that the observation group was not greatly different from the control group in adverse reactions including pernicious vomiting, myelosuppression, hypodynamia, rash, and liver function damage. Some studies have shown that bevacizumab combined with some drugs could lead to hypertension symptom in patients [19]. Some patients included in our study were accompanied by hypertension, but there was no new hypertension case after treatment.

Platelets are multifunctional cells, which can promote the development of some cancers and can be used as diagnostic and prognostic indicators for some cancers due to their abnormal expression [20]. The carcinogenesis of platelets is often induced by mediating platelet-related proteins such as TPO and P-selectin to mediate vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) [21, 22]. Therefore, the disease severity of the patients may be understood by detecting TPO and P-selectin. In order to find it out, we observed the changes of TPO and P-selectin expression in the two groups before and after treatment, finding that after treatment, the TPO and P-selectin expression in both groups decreased significantly and the expression of them in the observation group was significantly lower than that in the control group. A study by Wojtukiewicz et al. [23] pointed out that when VEGF was activated, the platelets could be much more adhesive, which promoted the development of cancer. Therefore, we postulated that bevacizumab, as a VEGF inhibitor, could suppress the activation of such platelets by inhibiting the activation of VEGF, and thus the expression of TPO and P-selectin was lower and the efficacy was better. In this study, we compared the TPO and P-selectin levels between the patients with remission and patients without remission in the observation group, finding that levels of TPO and P-selectin in the patients with remission were lower than those in the patients without remission. Subsequently, we drew ROC curves to analyze the predictive value of TPO and P-selectin for efficacy. It was shown that the AUC of TPO and P-selectin was 0.830 and 0.776, respectively, which further suggested that TPO and P-selectin may be predictive indexes for the efficacy of NSCLC. During treatment in our study, pernicious vomiting, myelosuppression, hypodynamia, rash, and liver function damage were found in both groups, but no big difference was discovered between the two groups in those aspects.

Table 5. ROC curve parameters

		AUC	95 CI%	Specificity	Sensitivity	Youden index	Cut-off
ROC for efficacy prediction	TPO	0.830	0.701-0.959	93.22%	60.00%	53.22%	>14.955
	P-selectin	0.776	0.659-0.893	47.46%	93.33%	40.79	>53.120
ROC for survival prediction	TPO	0.872	0.793-0.951	95.00%	62.96%	57.96	>12.125
	P-selectin	0.844	0.750-0.939	75.00%	83.33%	58.33	>50.065

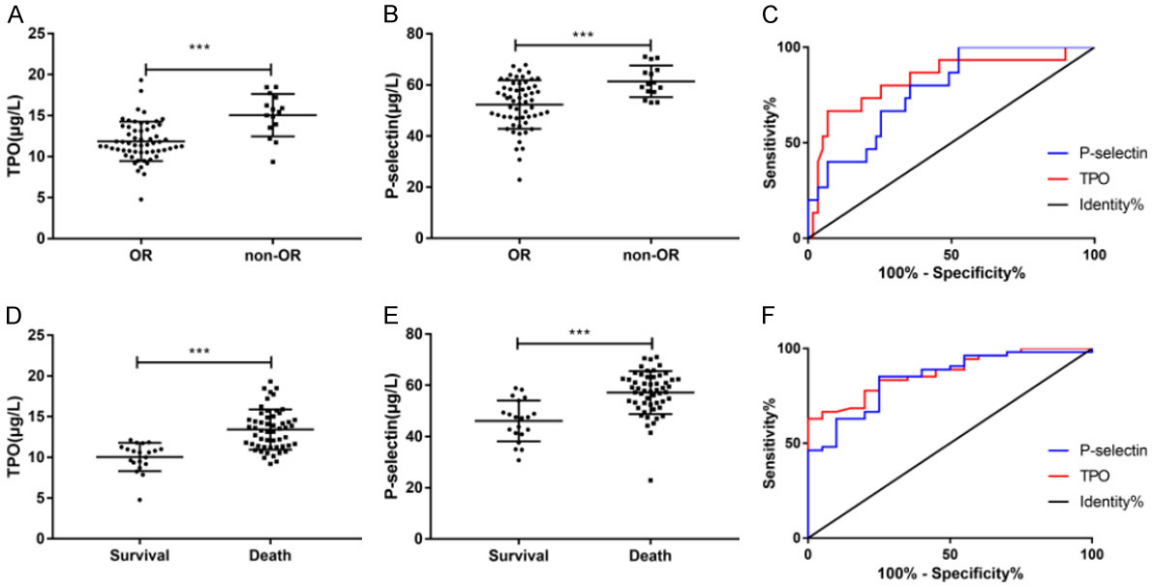

Figure 3. The expression of TPO and P-selectin in patients with different efficacy, and survived and dead patients. A. The expression of TPO in patients with remission was significantly lower than that in patients without remission (t=4.558, P<0.001). B. The expression of P-selectin in patients with remission was significantly lower than that in patients without remission (t=3.502, P<0.001). C. The AUC of TPO and P-selectin in predicting efficacy was 0.830 and 0.776, respectively. D. The expression of TPO in survived patients was significantly lower than that in dead patients (t=6.732, P<0.001). E. The expression of P-selectin in survived patients was significantly lower than that in dead patients (t=5.817, P<0.001). F. The AUC of TPO and P-selectin in predicting survival was 0.872 and 0.844, respectively.

We also followed up the patients for 3 years to analyze their survival, finding that the 3-year SR of the observation group was 27.03%, while that of the control group was 17.74%. Based on K-M curves, it can be found that the survival of the observation group was better than that of the control group, which also suggested that the bevacizumab combined with chemotherapy and radiotherapy was more effective than radiotherapy and chemotherapy along in prognosis of the patients. A study by Langer et al. [24] concluded that bevacizumab combined with chemotherapy could prolong the survival time of patients. We divided the patients into high expression groups and corresponding low expression groups according to the expression of TPO and P-selectin, respectively. The K-M curves showed that the SR of the two high expression groups was worse than that of the two low expression groups. Therefore, we postulated that the 3-year SR of the patients could be predicted by observing the expression of TPO and P-selectin in them. We compared the expression of TPO and P-selectin between the survived patients and the dead patients in the observation group, finding that the expression of them in the survived patients before treatment was dramatically lower than that in the control group. We also analyzed the value of TPO and P-selectin levels before treatment for forecasting the 3-year survival of patients through ROC curves. It was turned out that the AUC of TPO and P-selectin in predicting it was 0.872 and 0.844, respectively, which further indicated that TPO and P-selectin were expected to be predictive indicators of death of NSCLC patients.

However, there are still some deficiencies in this study. Firstly, the study has not included

normal healthy subjects for comparison, so the differences between patients and healthy people in TPO and P-selectin before and after treatment remain unclear. Secondly, the study has only determined the levels of TPO and P-selectin before and after treatment, and the expression changes of them for a longer time are unclear. Finally, we know that the expression of TPO and P-selectin has a certain relationship with the curative effect and prognosis of patients, but do not know the specific mechanism. Therefore, we hope to carry out corresponding research in the follow-up to support our point of view.

To sum up, bevacizumab can enhance the efficacy of chemotherapy and radiotherapy on NSCLC and lower the expression of TPO and P-selectin, and TPO and P-selectin are expected to be predictive indicators of efficacy and prognosis for patients.

Disclosure of conflict of interest

None.

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