Int J Clin Exp Med 2018;11(6):6062-6069
www.ijcem.com /ISSN:1940-5901/IJCEM0066365

Original Article

Efficacy and safety of Endostar combined with vinorelbine and cisplatin for the treatment of advanced non-small cell lung cancer: a comparative study

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Received September 28, 2017; Accepted February 8, 2018; Epub June 15, 2018; Published June 30, 2018

Abstract: This study aimed to investigate short- and long-term efficacy of continuous administration of Endostar (YH-16) combined with vinorelbine (NVB) and cisplatin (DDP) in the treatment of advanced non-small cell lung cancer (NSCLC). A total of 232 NSCLC patients were assigned into the YH-16 + NP group (n = 116, treatment with YH-16, NVB, and DDP) and NP group (n = 116, treatment with NVB and DDP). The rates of efficiency and clinical benefit, progression-free survival (PFS), adverse effects, and quality of life (QOL) were compared between the two groups. A multivariate Cox regression model was conducted for independent risk factors for prognosis of NSCLC. The rates of efficiency, clinical benefit, PFS, and median PFS were higher in the YH-16 + NP group than those in the NP group. The multivariate Cox regression model demonstrated that pathological classification, tumor-node-metastasis (TNM) staging, number of metastatic lesions, and treatment allocation were independent risk factors for prognosis of NSCLC. No statistical difference was observed in the incidence of adverse reactions. The Karnofsky performance scores were decreased both in the NP and YH-16 + NP groups before and after treatment while no significant difference was observed in KPS between these two groups. These findings indicate that compared with single NP regimen, the YH-16 + NP regimen shows better efficacy and safety in treatment of advanced NSCLC.

Keywords: Endostar, vinorelbine, cisplatin, advanced non-small cell lung cancer, chemotherapy, efficacy, safety

Introduction

Lung cancer is a leading cause of cancer-related mortality worldwide [1], accounting for more than 1.6 million deaths every year [2]. About 85% of patients with lung cancer have non-small cell lung cancer (NSCLC) and most of them are in the advanced stage at diagnosis [3]. The incidence of NSCLC is higher among men compared with women, accounting for 34% and 13.5% of all cancers, respectively. The age-standardized ratio for its incidence is 33.81%, among which 29.2% were men [4]. The 5-year survival for advanced NSCLC patients is 15% after diagnosis [1]. At present, platinum combined with a third-generation agent (paclitaxel, docetaxel, vinorelbine, pemetrexed, and gemcitabine) is the main treatment option for advanced NSCLC [5]. Although surgical excision and chemotherapy are attainable in some patients with advanced NSCLC, the therapeutic options for locally advanced or metastatic disease remain limited, presenting an urgent need for the development of new therapeutic combinations with improved efficacy and safety.

Combined chemotherapy of vinorelbine (NVB) and carboplatin is a regular chemotherapy regime for patients with lung cancers [6]. The NVB plus cisplatin (DDP) regime (NP) was proven to have the ability to increase survival time, with a promising response rate [6, 7]. However, cytotoxic chemotherapeutic agents kill both tumor cells and normal cells, inevitably leading to adverse reactions and poor QOL for patients with cancer after chemotherapy [7]. Therefore, exploring chemotherapy regimens with maximum efficacy and least adverse reactions are of great significance.

Endostar (YH-16) is a recombinant human endostatin that was approved as the first line drug for patients with non-small cell lung cancer (NSCLC) in China in 2005 [8]. Increasing evidence has shown that YH-16 is a useful anticancer drug in melanoma and liver cancer, due to its function of blocking tumor growth [8, 9]. Furthermore, YH-16 combined chemotherapy has turned out to be an effective regime for patients with advanced colorectal cancers [10, 11]. To the best of our knowledge, few research studies have paid close attention to the combination of YH-16 and NP chemotherapy, which may potentially be an effective anti-cancer therapy. Therefore, it is valuable to investigate the efficacy and safety of YH-16 combined with NP therapy in the treatment of advanced NSCLC.

Materials and methods

Ethics statement

The present study was performed with the approval of the Ethics Committee of Hainan General Hospital. All aspects of the study complied with the Declaration of Helsinki and informed consent was obtained from all study subjects before the examination.

Study subjects

The observational study subjects included 232 patients who were cytologically and/or pathologically diagnosed with NSCLC of stage III~IV and received curative chemotherapy in Hainan General Hospital from November 2011 to June 2014. Among the 232 enrolled patients, 164 were male and 68 were female, ranging from 33 to 75 years, with a mean age of (56.6 ± 8.6) years. 151 cases were under initial treatment and 81 cases under re-treatment. Inclusion criteria were as follows: (1) patients with measurable lesions and diagnosed by computed tomography (CT), type-B ultrasound and magnetic resonance imaging (MRI); (2) patients with normal blood and urine routine, hepatorenal and cardiopulmonary functions; (3) patients with a Karnofsky performance score (KPS) ≥ 60 points; (4) patients with expected survival time > 3 months; (5) patients with complete clinical data. Exclusion criteria were: (1) patients under other effective treatments at the moment; (2) patients with no measurable lesion or with unmeasurable lesions; (3) patients in pregnancy or lactation, or non-fertile patients; (4) patients with uncontrolled primary brain tumor or metastatic tumor in central nervous system; (5) patients having received radio-chemotherapy or biotherapy, or having been involved in other clinical test for drugs or instruments 30 days before the enrollment; (6) patients with persistent purulent wounds and lasting chronic and infectious wounds; (7) patients with a history of uncontrolled mental diseases. The 232 patients were randomly assigned into YH-16 + NP group (treated with YH-16 combined with NVB plus DDP chemotherapy) and NP group (treated with NVB plus DDP chemotherapy), with 116 cases in each group. Clinical data of patients were collected including age, gender, previous treatments, pathological classification, TNM staging, and number of metastatic lesions.

Treatments

Patients in the YH-16 + NP group received YH-16 (7.5 mg/m^2) and intravenous drip of sodium chloride physiological solution (500 mL) for 3~4 hours at an uniform speed from the 1st day to 14th day, once a day and repeat after 7 days' interval; NVB (25 mg/m^2) plus intravenous drip of NS (100 mL) on the 1st day and 5th day; and DDP (30 mg/m^2) plus intravenous drip of NS (500 mL) on 2rd day, 3rd day, and 4th day. For the NP group, patients only received the same administration of NVB and DDP as the YH-16 + NP group did. For both groups, the regimens were given at a 21st day course and the efficacy of the regimen efficacy was preliminarily evaluated after 2 courses and confirmed after 4 courses. Corresponding treatments were given when adverse effects, infection, or pain appeared.

Evaluation of efficacy

Efficacy was evaluated on basis of physical examination and MRI results and in accordance with Response Evaluation Criteria in Solid Tumors RECIST Version 1.1 [12] in terms of complete response (CR), all lesions disappeared completely; partial response (PR), the total of the maximum length of all lesions reduced by more than 30%; stable disease (SD), between PR and progressive disease (PD); and PD, compared with the minimum length of the lesion, the total of the maximum length of all the lesions increased by more than 20%.

Table 1. Comparison of baseline characteristics for patients in the YH-16 + NP and NP groups

Characteristics	YH-16 + NP group (n = 116)	NP group (n = 116)	*P*
Age (years)	57.4 ± 8.4	55.7 ± 8.9	0.136
Gender			
Female	83 (71.55)	81 (69.83)	0.773
Male	33 (28.45)	35 (30.17)	
Previous treatments			
Initial treatment	79 (68.10)	72 (62.07)	0.335
Re-treatment	37 (31.90)	44 (37.93)	
Pathological classification			
Squamous carcinoma	46 (39.66)	39 (33.62)	0.490
Adenocarcinoma	60 (51.72)	69 (59.48)	
Others	10 (8.62)	8 (6.90)	
TNM staging			
Stage III	71 (61.21)	60 (51.72)	0.145
Stage IV	45 (38.79)	56 (48.28)	
Number of metastatic lesions			
0	12 (10.34)	14 (12.07)	0.712
1	54 (46.55)	58 (50.00)	
≥ 2	50 (43.10)	44 (37.93)	

Note: YH-16 + NP group, the patients treated with YH-16 combined with NVB plus DDP chemotherapy; NP group, the patients treated with NVB plus DDP chemotherapy; YH-16, Endostar; NVB, vinorelbine; DDP, cisplatin; TNM, tumor-node-metastasis.

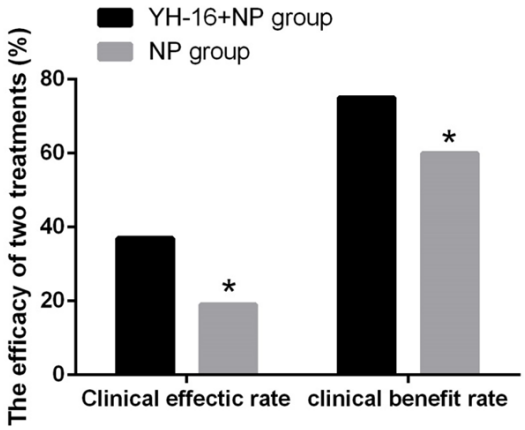

Figure 1. Comparison of short-term efficacy for patients in the YH-16 + NP and NP groups. Note: YH-16 + NP group, the patients treated with YH-16 (Endostar) combined with NVB (vinorelbine) plus DDP (cisplatin) chemotherapy; NP group, the patients treated with NVB plus DDP chemotherapy; YH-16, Endostar; NVB, vinorelbine; DDP, cisplatin.

The efficiency rate = number of cases with CR + PR/number of total cases × 100% and the clinical benefit rate = number of cases with (CR + PR + SD)/number of total cases × 100%.

Evaluation of adverse effects

Adverse effects were evaluated and graded according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0 by the United States National Cancer Institute (NCI) [13]. The incidence of severe adverse reactions in the two groups of patients were analyzed.

Follow up

Follow up was carried out from the date when patients started to receive treatment, by telephone or outpatient visit, once every two months until December 31, 2015. Duration from the date of patient receiving treatment to the date when confirmed as progression or death was defined as progression free survival (PFS). Patients who were lost to follow up or with no progression were recorded the last time when the patients were visited.

Evaluation of quality of life (QOL)

The QOL of patients with NSCLC was assessed based on the KPS system [14]. After treatment, KPS increasing by more than or equal to 10 points was considered improved. KPS fluctuating (increasing or decreasing) within 10 points was referred to as stable. KPS decreasing by more than 10 points was signified as deteriorated.

Statistical analyses

Data analysis was performed with SPSS 21.0 software (IBM Corp. Armonk, NY, USA). Measurement data are presented as mean ± standard deviation ($\bar{x}$ ± s) and testified by *t*-test. Count data were presented by percentage or rate and testified by Chi-square test. Kaplan-Meier curve was used to analyze efficacy of single factor and the Cox model was used to analyze the efficacy of multiple factors. *P* was a

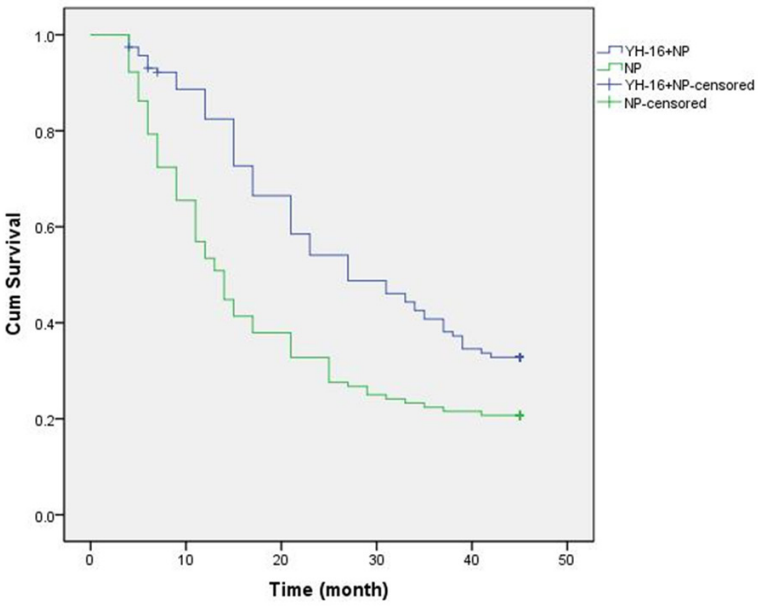

Figure 2. The PFS of patients in the YH-16 + NP and NP groups. Note: YH-16 + NP group, the patients treated with YH-16 (Endostar) combined with NVB (vinorelbine) plus DDP (cisplatin) chemotherapy; NP group, the patients treated with NVB plus DDP chemotherapy; YH-16, Endostar; NVB, vinorelbine; DDP, cisplatin; PFS, progression free survival.

two-tailed probability, with $P < 0.05$ indicating statistically significant.

Results

Baseline characteristics for patients in the YH-16 + NP and NP groups

There were no statistically significant differences in age, gender, previous treatments, pathological classification, TNM staging, and number of metastatic lesions between the two groups (all $P > 0.05$) (**Table 1**).

Short-term efficacy for patients in the YH-16 + NP and NP groups

In the YH-16 + NP group, no patients were detected with CR but 44 were detected with PR, 43 with SD, and 29 with PD. The efficiency and clinical benefit rates were 37.9% and 75.0%, respectively. In the NP group, no patients were found with CR, but 23 were found with PR, 47 with SD, and 46 with PD. The efficiency and clinical benefit rates were 19.8% and 60.3%, respectively. As shown in **Figure 1**, efficiency and clinical benefit rates were higher in the YH-16 + NP group than those in the NP group (both $P < 0.05$).

Long-term efficacy for patients in the YH-16 + NP and NP groups

Follow up was carried out in all patients, lasting for 4~45 months. Among the 116 patients in the YH-16 + NP group, 3 cases were lost to follow up, while no one was lost to follow up in the NP group. The median PFS were 27 months and 14 months in the YH-16 + NP and NP groups. Kaplan-Meier curve of PFS is shown in **Figure 2**, indicating that PFS of the YH-16 + NP group was higher than that of the NP group ($P < 0.05$).

Univariate survival analysis of the long-term efficacy of patients in the YH-16 + NP and NP groups

The factors that may influence median PFS including age, gender, previous treatments, pathological classification, TNM staging, and number of metastatic lesions were analyzed. The results show that the median PFS of the YH-16 + NP group was higher than that of the NP group ($P < 0.05$) (**Table 2**).

Multivariate survival analysis of the long-term efficacy of patients in the YH-16 + NP and NP groups

The Cox model was established with survival time (month) as a variable to analyze the effect of factors that influence PFS of patients with advanced NSCLC including age, gender, previous treatments, pathological classification, TNM staging, number of metastatic lesions, and treatment allocation. The results show that pathological type, TNM staging, number of metastatic lesions, and treatment allocation are independent prognostic factors of patients with advanced NSCLC (all $P < 0.05$) (**Table 3**).

Incidence of adverse effects for patients in the YH-16 + NP and NP groups

As shown in **Table 4**, no significant difference in incidence of the common severe adverse effects was found in the YH-16 + NP and NP

Table 2. Univariate survival analysis of median PFS of patients in the YH-16 + NP and NP groups

Variable	YH-16 + NP group (months)	NP group (months)	*P*
Age (years)			
≤ 50	27	15	0.002
> 50	21	11	0.019
Gender			
Female	27	14	0.002
Male	27	11	0.005
Previous treatments			
Initial treatment	27	15	*P* < 0.001
Re-treatment	23	11.5	0.044
Pathological types			
Squamous carcinoma	46	17	0.003
Adenocarcinoma	22	12	0.012
Others	32	8	0.039
TNM staging			
Stage III	33	15	0.001
Stage IV	17	12.5	0.031
Number of metastatic lesions (n)			
0	45	12	0.002
1	29	16	0.005
≥ 2	21	11	0.016

Note: YH-16 + NP group, the patients treated with YH-16 combined with NVB plus DDP chemotherapy; NP group, the patients treated with NVB plus DDP chemotherapy; YH-16, Endostar; NVB, vinorelbine; DDP, cisplatin; TNM, tumor-node-metastasis.

groups, including decreases in aleucocytosis, thrombocytopenia, hypoglycemia and nausea, and vomiting, muscle and joint pain, peripheral neuritis, diarrhea, constipation, hair loss, liver and renal dysfunction, or electrocardiographic abnormality (all $P > 0.05$). There were no treatment related deaths in either the YH-16 + NP or NP groups.

Change of QOL in the YH-16 + NP and NP groups before and after treatment

The changes of QOL in the YH-16 + NP and NP groups are presented in **Table 5**. In the YH-16 + NP group, 35.3% (41/116) of the patients had improved QOL; 27.6% (32/116) had no change; and 37.1% (43/116) had deteriorated QOL. In the NP group, 29.3% (34/116) of the patients had better QOL; 38.8% (45/116) had no change; and 31.9% (37/116) had deteriorated QOL. The mean KPS decreased by 3.1 points in the YH-16 + NP group and decreased by 2.1 points in the NP group. The difference was not statistically significant ($P > 0.05$). The results indicate that compared with single NP regimen, YH-16 + NP regimen has better safety in treatment of advanced NSCLC.

Discussion

Cytotoxicity of chemotherapeutic agents has long been an obstacle in cancer treatment with chemotherapy, which leads to poor QOL of the patients who received chemotherapy [6]. Thus, a method of killing more cancer cells and less normal cells could be an effective solution in improving the safety and efficacy of chemotherapy as well as QOL under chemotherapy. Several studies treating tumor cells as targets in cancer therapy have demonstrated that anti-angiogenic "vessel normalizing" of YH-16 was a promising anti-cancer strategy to bring higher cancer cell death and silence metastasis [8, 15, 16]. In our study, patients with advanced NSCLC were enrolled and treated with two therapy strategies. YH-16 was combined with NP and then single NP to compare and evaluate their efficacy and safety for NSCLC treatment.

Initially, our study revealed that efficiency and clinical benefit rates were higher in the YH-16 + NP group than those in the NP group. YH-16 as a kind of endostatin is believed to be internalized by endothelial cells [17]. Increasing evidence has shown that YH-16 could antagonize VEGF-induced tumor angiogenesis [8-10]. Through creating temperate normalization of tumor vasculature for the delivery of chemotherapeutic agents, YH-16 brings higher death rates of cancer cells and minimal toxicity [18]. NVB, namely an anticancer drug, often has resulted in vascular injury such as vascular pain, phlebitis, venous irritation, and necrotizing vasculitis. One study clearly demonstrated that VNR was able to induce oxidative stress through increasing production of intracellular reactive oxygen species (ROS) and depleting

Table 3. Multivariate survival analysis of median PFS of patients in the YH-16 + NP and NP groups

Variable	β	SE	Wald	*P*	OR	95% CI
Age	0.464	0.186	6.192	*0.013*	1.59	1.104-2.292
Gender	0.25	0.172	2.112	*0.146*	1.283	0.917-1.797
Previous treatments	0.235	0.165	2.026	*0.155*	1.265	0.915-1.748
Previous treatments	0.235	0.165	2.026	*0.155*	1.265	0.915-1.748
Pathological types	0.395	0.128	9.511	*0.002*	1.484	1.155-1.907
TNM staging	0.327	0.159	4.245	*0.039*	1.387	1.016-1.893
Number of metastatic lesions	0.259	0.123	4.447	*0.035*	1.296	1.018-1.650
Treatment allocation	0.531	0.159	11.187	*0.001*	1.7	1.246-2.321

Note: SE, standard error; OR, odds ratio; CI, confidence interval; YH-16 + NP group, the patients treated with YH-16 combined with NVB plus DDP chemotherapy; NP group, the patients treated with NVB plus DDP chemotherapy; YH-16, Endostar; NVB, vinorelbine; DDP, cisplatin; TNM, tumor-node-metastasis.

Table 4. Comparison of the incidence of adverse effects for patients in the YH-16 + NP and NP groups

Adverse effects	Level III		Level IV		Level III + IV		P^a
	YH-16 + NP group	NP group	YH-16 + NP group	NP group	YH-16 + NP group	NP group	
Leukopenia	10 (8.6%)	12 (10.3%)	4 (3.4%)	6 (5.2%)	14 (12.1%)	18 (15.5%)	0.446
Thrombocytopenia	4 (3.4%)	6 (5.2%)	1 (0.9%)	2 (1.7%)	5 (4.3%)	8 (6.9%)	0.392
Hypoglycemia	7 (6.0%)	10 (8.6%)	1 (0.9%)	3 (2.6%)	8 (6.9%)	13 (11.2%)	0.253
Nausea and vomiting	13 (11.2%)	12 (10.3%)	5 (4.3%)	9 (7.8%)	18 (15.5%)	21 (18.1%)	0.598
Muscle and joint pain	6 (5.2%)	8 (6.9%)	0 (0.0%)	1 (0.9%)	6 (5.2%)	9 (7.8%)	0.423
Peripheral neuritis	3 (2.6%)	2 (1.7%)	1 (0.9%)	5 (4.3%)	4 (3.4%)	7 (6.0%)	0.354
Diarrhea	8 (6.9%)	9 (7.8%)	5 (4.3%)	7 (6.0%)	13 (11.2%)	16 (13.8%)	0.552
Constipation	18 (15.5%)	21 (18.1%)	2 (1.7%)	4 (3.4%)	20 (17.2%)	25 (21.6%)	0.406
Hair loss	20 (17.2%)	23 (19.8%)	7 (6.0%)	8 (6.9%)	27 (23.3%)	31 (26.7%)	0.544
Allergic reactions	8 (6.9%)	6 (5.2%)	1 (0.9%)	5 (4.3%)	9 (7.8%)	11 (9.5%)	0.640
Liver dysfunction	20 (17.2%)	23 (19.8%)	9 (7.8%)	10 (8.6%)	29 (25.0%)	33 (28.4%)	0.553
Renal dysfunction	2 (1.7%)	7 (6.0%)	6 (5.2%)	8 (6.9%)	8 (6.9%)	15 (12.9%)	0.124
Electrocardiographic abnormality	12 (10.3%)	10 (8.6%)	4 (3.4%)	9 (7.8%)	16 (13.8%)	19 (16.4%)	0.582

Note: P^a, comparing the adverse effects of level III + IV between the NP and YH-16 + NP groups; YH-16 + NP group, the patients treated with YH-16 combined with NVB plus DDP chemotherapy; NP group, the patients treated with NVB plus DDP chemotherapy; YH-16, Endostar; NVB, vinorelbine; DDP, cisplatin; TNM, tumor-node-metastasis.

Table 5. Change of quality of life in the YH-16 + NP and NP groups before and after treatment

	KPS											Mean value	*P*
YH-16 + NP group	0	10	20	30	40	50	60	70	80	90	100		0.773
Before treatment	0	0	0	0	0	0	18	39	26	32	1	76.5 ± 10.7	
After treatment	0	0	0	1	3	9	15	34	23	30	1	73.4 ± 14.2	
NP group	0	10	20	30	40	50	60	70	80	90	100		
Before treatment	0	0	0	0	0	0	21	40	28	22	5	75.7 ± 11.2	
After treatment	0	0	1	3	4	12	14	21	17	42	2	73.4 ± 17.7	

Note: KPS, Karnofsky performance scores; YH-16 + NP group, the patients treated with YH-16 combined with NVB plus DDP chemotherapy; NP group, the patients treated with NVB plus DDP chemotherapy; YH-16, Endostar; NVB, vinorelbine; DDP, cisplatin; TNM, tumor-node-metastasis.

intracellular glutathione (GSH) in porcine aorta endothelial cells [19]. Cisplatin also has been treated as one of the most widely adapted anti-cancer agents [20]. Besides, the PFS and median PFS of patients in the YH-16 + NP group was significantly higher than that of the patients in

the NP group, indicating that tumor growth of patients in the YH-16 + NP group was better controlled than that in the NP group. PFS is increasingly adapted rather than overall survival (OS) as the efficacy end point in the trials of metastatic renal cell cancer (mRCC) [21]. It was used as an attractive end point due to the fact that it was available earlier than OS [22]. Tumor progression in patients with non-small cell lung cancer (NSCLC) is in close correlation with significant worsening in health-related quality of life, which confirms the value of PFS being treated as a typical patient-relevant end point [23]. Importantly, one study mentioned that uncommon epidermal growth factor receptor (EGFR) mutations, more sites of distal metastasis, and poor performance status were independently associated with poor PFS, demonstrating PFS prognosis effects on EGFR-mutant patients [24]. In our study, PFS was adapted as an end point for NSCLC. An increased PFS as well as median PFS were observed in our study, thus, we reached the conclusion that YH-16 combined with NP and single NP can promote efficacy and safety for NSCLC treatment.

Importantly, the multivariate Cox regression model demonstrates that pathological classification, TNM staging, number of metastatic lesions, and treatment allocation are independent risk factors for prognosis of NSCLC. The lung cancer TNM staging system has been modified since it was first edited in the late 1960s, which was then often used for cancer conditions [25]. Metastatic lesions of primary tumors, often originated in various parts of the body, consist of almost 1% of oral cancers, which can influence both bones and soft tissues in the maxillofacial region [26]. These data were in correspondence with our findings. Thus, we verified the effects of YH-16 combined with NP.

Conclusion

In conclusion, the results of our study suggest that YH-16 is an effective anti-cancer drug, aiding in the maximization of efficacy with less adverse effects of chemotherapy. In future efforts, the value of YH-16 will be more precisely assessed. Of course, there are limitations to our study. Though powerful evidence was presented in our study, the reliability of the results may be impaired by the less objective methods used and small sample size when our study is used as a reference for future studies on a single cancer.

Acknowledgements

This study was supported by Key Science and Technology Projects of Hainan Province (ZDYF20-16112) and the National Natural Science Foundation of China (81760-255). We would like to acknowledge the reviewers for their helpful comments on this paper.

Disclosure of conflict of interest

None.

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