Am J Transl Res 2021;13(9):10809-10815
www.ajtr.org /ISSN:1943-8141/AJTR0127724

Original Article

Effect of thalidomide combined with TP chemotherapy on serum VEGF and NRP-1 levels advanced esophageal cancer patients

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Received December 6, 2020; Accepted January 21, 2021; Epub September 15, 2021; Published September 30, 2021

Abstract: Objective: This study aimed to investigate the effect of thalidomide combined with pacilitaxel plus cisplatin (TP) chemotherapy on serum vascular endothelial growth factor (VEGF) and neuropilin-1 (NRP-1) levels in advanced esophageal cancer patients. Method: A total of 133 patients with advanced esophageal cancer receiving treatment in Danzhou People's Hospital from February 2017 to July 2019 were recruited and divided into a control group (CG, n = 53) and a study group (SG, n = 80) randomly. Patients in the CG (53 cases) were treated with TP chemotherapy, and patients in the SG (80 cases) were treated with thalidomide on the basis above. The general data of the two groups of patients was observed, as well as the therapeutic effect, chemotherapy-related toxicity, and quality of life. Serum vascular endothelial growth factor (VEGF) and neuropilin-1 (NRP-1) levels were tested before and after treatment. Results: There was no difference in general data between the two groups (P>0.05), and the occurrence of nausea and vomiting in SG was significantly lower than those in CG (P<0.05). The therapeutic effect was better in SG than CG (P<0.05). The Karnofsky Performance Scale (KPS) score improvement rate, appetite increase rate and body weight increase rate in SG were better than those in CG (P<0.05). After treatment, compared with CG, SG had lower serum VEGF and NRP-1 levels (P<0.05) and better quality of life (P<0.05). Conclusion: Thalidomide combined with TP chemotherapy is safe and effective in treating advanced esophageal cancer patients, which reduces patients' serumlevels of VEGF and NRP-1.

Keywords: Thalidomide, TP chemotherapy, advanced esophageal cancer

Introduction

Esophageal cancer is a significant cause of cancer-related death. It was estimated that about 572,000 cases of esophageal cancer were diagnosed worldwide in 2018 [1]. Globally, the mortality rate (5.3%) of esophageal cancer patients is higher than the incidence rate (3.2%) [2]. Primary esophageal cancer can be classified as esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC) [3]. Smoking, drinking, obesity, gender and gastroesophageal reflux disease may be risk factors for esophageal cancer [4]. Surgical treatment, chemotherapy and chemoradiotherapy have been proved to be effective methods in improving patients'survival outcome and quality of life [5]. The team of Zhu [6] proposed that paclitaxel plus cisplatin (TP) chemotherapy combined with radiotherapy can improve the 5-year survival outcome of esophageal cancer patients with effect. Liu et al. [7] indicated that TP chemotherapy in combination with 5-fluorouracil plus cisplatin (CF) chemotherapy were effective strategies for advanced esophageal cancer treatment, and TP chemotherapy has better median progression-free survival (PFS) outcome. Although TP chemotherapy has a good therapeutic effect on esophageal cancer, it may still cause adverse reactions such as vomiting and nausea. Vomiting and nausea caused by chemotherapy may reduce chemotherapy effect [8], therefore, there is an urgent need for a proper vomit-stopping regimen for advanced esophageal cancer chemotherapy.

Thalidomide is a glutamic acid derivative that can be utilized as a sedative to treat vomiting

during pregnancy [9]. It has an anti-angiogenic effect, and plays a significantrole in treating various solid tumors [10]. A randomized controlled study [11] indicated that thalidomide could improve the prognosis of advanced esophageal cancer patients who received local radiotherapy. Wang et al. [12] suggested that thalidomide can regulate the formation and growth of breast cancer malignancy via suppressing angiogenesis. Chen et al. [13] applied nanoparticles to load thalidomide, and found that thalidomide can effectively suppress angiogenesis and tumor growth of lung cancer. It is believed that thalidomide can efficiently relieve the pain degree of bone cancer pain in mice [14], and can enhance the delivery efficiency and therapeutic effect of cisplatin in solid tumors through promoting vascular system remodeling [15].

At present, only a few studies focus on thalidomide combined with TP chemotherapy in treating advanced esophageal cancer. Here, 133 advanced esophageal cancer patients were divided into a control group (CG, n = 53) and a study group (SG, n = 80) according to different treatment methods. CG adopted TP chemotherapy, and SG adopted thalidomide on the basis above. Here, we investigated the safety and effectiveness of thalidomide combined with TP chemotherapy in advanced esophageal cancer, thus to provide reliable scientific research data for chemotherapy strategy of the disease. In addition, since thalidomide has significant anti-angiogenesis effect, and serum vascular endothelial growth factor (VEGF) and neuropilin-1 (NRP-1) are involved in tumor angiogenesis, the impacts of thalidomide combined with TP chemotherapy regimen on VEGF and NRP-1 are also discussed in the study.

Methods

General data

A total of 133 advanced esophageal cancer patients were assigned to a control group (CG, n = 53) and a study group (SG, n = 80) according to different treatment methods. CG adopted TP chemotherapy, and SG adopted thalidomide on the basis above. CG consisted of 53 cases of patients (38 males and 15 females), aged 59.52±10.19 years, including 42 cases with ESCC and 11 cases with adenocarcinoma. SG consisted of 80 cases of patients (64 males and 16 females), aged 60.76±9.77 years, including 59 cases with ESCC and 21 cases with adenocarcinoma. There was no statistical difference in gender, age, histological subtype, smoking history, alcoholism history and tumor stage between CG and SG. More details are shown in **Table 1**.

Inclusion and exclusion criteria

Cases were included according to the following criteria: patients with esophageal cancer diagnosed histologically; patients in TNM stage IIIA-IV; patients under 75 years of age; patients' Karnofsky's performance scale (KPS) score was not less than 80 points; patients' neutrophil count was not less than 1.5×10^9/L, white blood cell count not less than 3×10^9/L, and platelet count not less than 1×10^{11}/L; patients' survival time after diagnosis was longer than 3 months. Cases were excluded according to the following criteria: patients received surgical resection of lesions, chemotherapy or radiotherapy; patients complicated with esophageal perforation, severe liver or kidney injury, cardiopulmonary disease, or mental disorder; patients in pregnancy or lactation period; patients were allergic to thalidomide, paclitaxel or cisplatin. In line with the *Declaration of Helsinki*, this study informed all subjects of the research information, and obtained the written informed consent of the subjects and the ethical approval of the research institution.

Treatment methods

After admission, both groups of patients received basic symptomatic treatment and chemotherapy, as well as dexamethasone to prevent allergy. On this basis, CG adopted TP chemotherapy. On the first day, paclitaxel injections (Hainan Choitec Pharmaceuticals Co., Ltd., SFDA approval number: H20057065, 5 mL: 30 mg) were given intravenously, as well as 175 mg/m^2+500 mL 0.9% sodium chloride injections, which was completed within 3 hours. Day 2-4: Cisplatin injections (Qilu Pharmaceutical Co., Ltd., SFDA approval number: H20023461, 20 mg) were given intravenously, as well as 25 mg/m^2+500 ml of 0.9% sodium chloride injections, with a circle of 21 days, 4 cycles in total. SG adopted thalidomide tablets (Changzhou Pharmaceutical Co.,

Table 1. General data

	CG n = 53	SG n = 80	*P* value	χ^2/t
Gender				
Male	38	64	0.268	1.229
Female	15	16		
Age	59.52±10.19	60.76±9.77	0.482	0.704
Histological subtypes			0.498	0.527
Squamous cell carcinoma	42	59		
Adenocarcinoma	11	21		
Smoking history			0.454	0.561
Present	24	31		
Absent	29	49		
Alcoholism history			0.301	1.073
Present	21	39		
Absent	32	41		
T stage			0.491	0.476
T3	14	17		
T4a/b	39	63		
N stage			0.301	2.402
N1	8	7		
N2	34	61		
N3	11	12		
M stage			0.467	0.514
M0	16	23		
M1	37	57		
TNM stage			0.403	1.817
IIIB	7	11		
IIIC	9	12		
IV	37	57		
Serum VEGF (pg/ml)	498.33±57.91	486.98±56.17	0.262	1.127
Serum NRP-1 (ng/ml)	2.85±0.67	2.99±0.61	0.215	1.246

Ltd., SFDA approval number: H32026130, 50 mg) on the basis of treatment methods used in CG, with 100 mg a time, once a day, for 3 months.

Outcome measures

The events of leukopenia, neutropenia and thrombocytopenia were counted and analyzed. The cases with nausea and vomiting in the two groups were recorded, as well as the cases with hepatic injury, esophageal injury and muscle pain. Therapeutic effect, improvement of KPS score (the scoring criteria are shown in **Table 2**), increase in appetite, and the number of cases with increased body mass were compared between the two groups. The quality of life of the two groups of patients was counted before and after treatment. Venous blood samples were obtained before and after treatment to determine serum vascular endothelial growth factor (VEGF) and neuropilin-1 (NRP-1) levels using ELISA (Abcam, ab222510&ab227901).

Statistics and analysis

SPSS 22.0 software was applied for data statistical analysis, and Graphpad8.0 for plotting. The measurement data was expressed by mean ± SD, and the counting data by n (%). Whether the data conformed to normal distribution was verified by K-S test. The independent sample t test and chi-square test were utilized for statistical difference analysis. Taking 95% as its confidence interval, the difference was statistically significant when $P<0.05$.

Table 2. KPS scoring criteria

Performance status	Score
Normal no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs or symptoms of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self; unable to carry on normal activity or to do active work	70
Requires occasional assistance, but is able to care for most of his personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospital admission is indicated although death not imminent	30
Very sick; hospital admission necessary; active supportive treatment necessary	20
Moribund; fatal processes progressing rapidly	10
Dead	0

Table 3. Therapeutic effect

	CG n = 53	SG n = 80	χ^2	*P* value
CR	2 (3.77)	6 (6.25)		
PR	24 (45.28)	47 (58.75)		
SD	13 (24.53)	10 (12.50)		
PD	17 (32.08)	17 (21.25)		
Remission rate	26 (49.06)	53 (66.25)	3.908	0.048
Disease control rate	36 (67.92)	63 (78.75)	4.571	0.033

Table 4. Chemotherapy-related toxicity

	CG n = 53	SG n = 80	χ^2	*P* value
Hematology			1.534	0.125
Leukopenia	9 (16.98)	11 (13.75)		
Neutropenia	13 (24.53)	10 (12.50)		
Thrombocytopenia	5 (9.43)	9 (11.25)		
Gastrointestinal tract			2.250	0.025
Nausea	6 (11.32)	3 (3.75)		
Vomiting	7 (13.21)	5 (6.25)		
Hepatic injury	4 (7.55)	3 (3.75)	0.922	0.337
Esophageal injury	5 (9.43)	7 (8.75)	0.893	0.135
Muscle pain	13 (24.53)	11 (13.75)	1.582	0.114

Results

Clinical efficacy and safety of thalidomide combined with TP chemotherapy in treating advanced esophageal cancer patients

The therapeutic effects of the two groups of patients were counted. In CG, there were 2 cases of complete response (CR), 24 cases of partial response (PR), 13 cases of stable disease (SD) and 17 cases of progressive disease (PD), with a remission rate of 49.06% and a disease control rate of 67.92%. In SG, the number of cases with CR, PR, SD and PD were 6, 47, 10, and 17, respectively, with a remission rate of 66.25% and a disease control rate of 78.75%. The remission rate and disease control rate in the SG were statistically higher than those in CG ($P_{\text{remission rate}} = 0.048$, $P_{\text{disease control rate}} = 0.033$). These results indicate that thalidomide plus TP chemotherapy can effectively treat advanced esophageal cancer patients (**Table 3**).

We also counted the chemotherapy-related toxicity of the two groups. **Table 4** shows that there were 27 cases of hematological events, 13 cases of nausea and vomiting, 4 cases of hepatic injury, 5 cases of esophageal injury and 13 cases of muscle pain in CG. In SG, however, there were 30 hematological events, 8 nausea and vomiting, 3 hepatic injury, 7 esophageal injury and 11 muscle pain. The number of nausea and vomiting cases in the SG was statistically lower than that in the CG ($P = 0.025$). The above results demonstrate that thalidomide plus TP chemotherapy is safe, which can reduce the occurrence of nausea and vomiting in advanced esophageal cancer patients.

Impact of thalidomide combined with TP chemotherapy on life quality and quality of life of advanced esophageal cancer patients

In this paper, life quality of patients in both groups was assessed from improvement of KPS score and increases in appetite and body mass. **Table 5** demonstrates that in CG, 30

Table 5. Life quality

	CG n = 53	SG n = 80	χ^2	*P* value
Improvement in KPS score	30 (56.60)	59 (73.75)	2.058	0.039
Increase in appetite	28 (52.83)	61 (76.25)	2.810	0.005
Increase in body mass	32 (60.38)	62 (77.50)	2.124	0.034

Table 6. Quality of life

	SG n = 80	CG n = 53	t	*P* value
Physiological field	20.66±4.68	18.09±5.12	2.931	0.004
Psychological field	21.53±5.29	19.21±5.66	2.375	0.019
Social relation field	9.25±2.07	8.06±2.11	3.208	0.017
Environmental field	20.28±4.89	22.21±5.07	2.180	0.031
Total score of quality of life	72.53±12.08	67.52±10.62	2.521	0.013

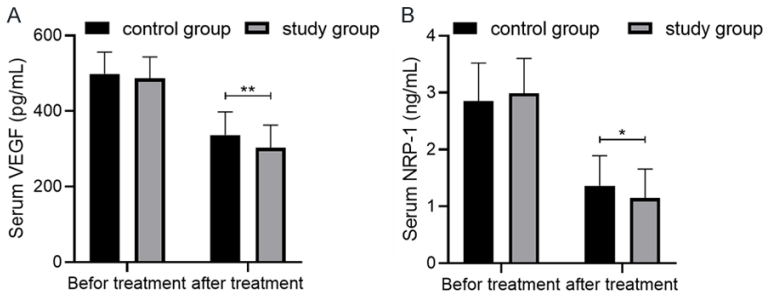

Figure 1. Comparison of serum VEGF and NRP-1 levels between the two groups. A. After treatment, serum VEGF in SG is lower than that in CG. B. After treatment, serum NRP-1 in SG is lower than that in CG. *P<0.05, **P<0.01. Study group n = 80, control group n = 53.

cases had improved KPS scores, 28 cases had increased appetite, and 32 cases had increased body weight. In SG, KPS scores improved in 59 cases, appetite increased in 61 cases, and body weight increased in 62 cases. All the three indexes in SG were better than those in CG, revealing that thalidomide combined with TP chemotherapy is beneficial to improve patient life quality.

Patients' quality of life scores were also calculated at the last follow-up. **Table 6** shows that CG scored 20.66±4.68 points in physiological field, 21.53±5.29 points in psychological field, 9.25±2.07 points in social relation field, and 20.28±4.89 points in environmental field, with a total score of 72.53±12.08 points. In SG, the scores were 18.09±5.12 points in physiological field, 19.21±5.66 points in psychological field, 8.06±2.11 points in social relation field and 22.21±5.07 points in environmental field, with a total score of 67.52±10.62 points. Each score in SG was statistically higher than that in CG. These results suggest that thalidomide combined with TP chemotherapy can better improve the quality of life.

VEGF and NRP-1 levels

Thalidomide has remarkable anti-angiogenesis effect, and VEGF and NRP-1 are involved in tumor angiogenesis. Therefore, serum VEGF and NRP-1 levels were applied to assess the anti-angiogenic effect of the two treatment regimens. **Figure 1** indicates that VEGF and NRP-1 levels reduced in both groups statistically after treatment in comparison with those before treatment. And when compared with CG, SG had lower serum VEGF and NRP-1 levels. The above results reveal that thalidomide plus TP chemotherapy can achieve better effects in inhibiting serum VEGF and NRP-1.

Discussion

Thalidomide has medicinal value in treating numerous diseases. Chen et al. [16] stated that thalidomide has potential application value in treating hypersplenism complicated with thrombocytopenia caused by liver cirrhosis or thalassemia. In Crohn's disease, thalidomide may achieve its therapeutic effect through improving TH17/Treg cell imbalance and intestinal fibrosis [17]. Besides, it has potential application value in anti-tumor therapy [18, 19]. Here, compared with CG, the remission rate and disease control rate of SG were statistically higher than those of CG, proving better treatment effect of thalidomide combined with TP chemotherapy in advanced esophageal cancer.

Chemotherapy-related toxicity results also uncovered that thalidomide combined with TP chemotherapy is more effective in improving vomiting and nausea. Thalidomide has been proved to play an important role in relieving

vomiting and nausea. For example, Zhang et al. [20] revealed that thalidomide in combination with palonosetron and dexamethasone can significantly improve nausea and vomiting of chemotherapy patients, and Yu et al. [21] put forward that thalidomide can prevent nausea and vomiting induced by chemotherap, without producing serious toxic and side effects.

As an important biological process in tumors, angiogenesis is requiree for malignant tumor growth [22]. Anti-angiogenesis strategy has gradually become a research hotspot in tumor therapy [23]. VEGF and its receptor are a representative angiogenesis pathway [24], and inhibition of this pathway has promising applications and prospects in antitumor therapy [25-27]. NRP-1 protein is also closely associated with angiogenesis. Wang et al. [28] proposed that NRP-1 promotes angiogenesis of liver cancer through VEGFR2-mediated angiogenesis pathway. In addition, there is also a study [29] which showed that NPR-1 is an essential factor for normal or pathological retinal angiogenesis. According to this paper, serum VEGF and NRP-1 levels in the two groups were lower than those before treatment. After treatment, the levels of serum VEGF and NRP-1 in SG were lower than those in CG. Shen et al. [15] reported that thalidomide regulates the formation and growth of tumor blood vessels through angiogenesis-related factors in endothelial cells and tumor cells. Therefore, it is speculated that thalidomide plus TP chemotherapy may be more beneficial to block tumor angiogenesis via VEGF and NRP-1 in advanced esophageal cancer.

Although this paper discusses the safety and effectiveness of thalidomide plus TP chemotherapy in treating advanced esophageal cancer from the aspects of therapeutic effect, chemotherapy-related toxicity, and quality of life, there are still some shortcomings. This paper did not optimize the dosage of thalidomide, whose optimal conditions combined with TP chemotherapy will therefore be discussed in future studies. Besides, since we did not include more samples and observation indicators, the potential application value of thalidomide plus TP chemotherapy in advanced esophageal cancer was not fully explored. Furthermore, risk factors that may influence the survival outcome of advanced esophageal cancer were not discussed.

To sum up, thalidomide in combination with TP chemotherapy is safe and effective for advanced esophageal cancer treatment. In addition, this regimen may inhibit tumor angiogenesis via reducing serum VEGF and NRP-1 levels. And thalidomide plus TP chemotherapy is worthy of further study and clinical promotion.

Disclosure of conflict of interest

None.

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