Am J Transl Res 2021;13(8):9802-9807
www.ajtr.org /ISSN:1943-8141/AJTR0131727

Original Article

The effects of albumin-bound paclitaxel combined with cisplatin injections on patients with advanced laryngeal cancer and serum survivin

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Received February 9, 2021; Accepted April 23, 2021; Epub August 15, 2021; Published August 30, 2021

Abstract: Objective: To explore the effects of the TP (Taxol plus Platinol) regimen and the PF (Platinol plus fluorouracil) regimen on patients with advanced laryngeal cancer and on the patients' VEGF-C (vascular endothelial growth factor C) and survivin genes. Methods: 42 patients with locally advanced laryngeal cancer treated in our hospital from June 2018 to October 2020 were recruited as the study cohort. The patients were assigned into a control group (21 cases) or an observation group (21 cases). The control group was administered the PF regimen, and the observation group was administered the TP regimen. Both groups were treated for four consecutive courses. The clinical efficacy of the two groups of patients was observed, and the two groups' treatment effects, their serum VEGF-C, and survivin levels, and their adverse reactions were compared. Results: A superior clinical efficacy was observed in the observation group (85.7%) than in the control group (57.1%) ($P<0.05$). Before the treatment, the two groups' serum VEGF-C and survivin levels showed no significant differences ($P>0.05$). After the treatment, apparently lower serum VEGF-C and survivin levels in the observation group were measured, and both groups witnessed a decline in their levels ($P<0.05$). We measured higher overall survival times and tumor-free survival times in the patients in the observation group compared to the control group ($P<0.05$). There was no significant difference in the incidences of adverse reactions between the two groups of patients ($P>0.05$). Conclusion: The TP regimen in the treatment of laryngeal cancer can reduce the VEGF-C and survivin levels in patients and has a better therapeutic effect, so it is worthy of clinical promotion.

Keywords: Cisplatin, albumin-bound paclitaxel, chemotherapy, efficacy, survivin

Introduction

Laryngeal cancer is a type of malignant tumor that is frequently diagnosed in China. In early laryngeal cancer, surgical and radiation treatment are equally effective. However, in advanced laryngeal cancer, radiation treatment is more effective than surgery [1]. Accordingly, in the treatment of locally advanced laryngeal cancer, chemotherapy and concurrent radiotherapy are commonly used clinical treatment methods, and they have reached a 5-year survival rate of 10% to 40% [2]. The PF regimen is the standard chemotherapy regimen for concurrent radiotherapy and chemotherapy for laryngeal cancer, but its effect is undermined by its inability to prolong overall patient survival [3]. By comparison, the TP regimen has been shown to be more efficacious in medical research results. The survivin gene is a known apoptosis-suppressing gene, and it has the dual functions of inhibiting cell apoptosis and regulating cell division. Survivin protein is widely expressed in a variety of malignant tumors, and the high expression of the survivin protein can inhibit tumor cell apoptosis and promote tumor cell proliferation [4]. Therefore, this study explores the effect of albumin-bound paclitaxel combined with cisplatin injections on patients with advanced laryngeal cancer and the combination's effect on patients' VEGF-C and survivin gene levels in patients, so as to provide a scientific basis for clinical treatment.

Materials and methods

General materials

42 patients with locally advanced laryngeal cancer admitted to the Department of

Otolaryngology in our hospital from June 2018 to October 2020 were recruited for this study. All the patients underwent a comprehensive physical examination, including biochemical tests, liver ultrasound, and throat CT or MRI before their treatment. The patients' estimated survival times were more than three months, and they all provided written informed consent, and patients with abnormal liver or kidney function were excluded. According to the treatment method each patient was administered, the patients were divided into the observation group (21 cases in TP regimen group) and the control group (21 cases in the PE regimen group). There were 13 males and 8 females in the observation group, and they ranged in age from 45 to 65 years old, with a mean age of (53.95±5.98) years old. In terms of the TNM staging, 10 patients had stage III cancer and 11 patients had stage IV cancer. In the control group, there were 12 males and 9 females, ranging in age between 45 and 65 years old, with a mean age of (54.14±5.25) years old. In terms of TNM staging, 11 patients were stage III and 10 patients were stage IV. The general clinical data of the two groups of patients were comparable (P>0.05). Ethical approval was granted by the ethics committee of our hospital.

Inclusion criteria

(1) Patients between 18 and 65 years old, (2) Patients with advanced laryngeal cancer confirmed by histology and or cytology, (3) Clinical stage: t3-4n0-3m0 stage of laryngeal cancer (AJCC 8th Edition), and (4) The patients were informed of the basic content of the study and signed the informed consent.

Exclusion criteria

(1) Patients with other malignant tumors, (2) Patients with known or suspected autoimmune diseases or severe mental health diseases, (3) Pregnant or lactating women, (4) Patients younger than 18 or older than 65 years old, and (5) Patients with previous history of severe hypersensitivity to any component of albumin-bound paclitaxel combined or cisplatin.

Chemotherapy: (1) Observation group. The patients routinely took dexamethasone, cimetidine, etc., and then they were given an intravenous infusion of 135 mg/m^2 paclitaxel [Produced by Bristol-Myers Squibb (China) Investment Co., Ltd.] for at least 3 hours on the first day and an intravenous infusion of 25 mg/m^2 cisplatin (produced by Yunnan Gejiu Biological Pharmaceutical Co., Ltd.) on days 1 to day 3. Four weeks was a cycle.

(2) Control group. The patients were administered an intravenous infusion of 25 mg/m^2 of cisplatin on the first to third days and an intravenous infusion of 500 mg/m^2 of fluorouracil on days 1 to 5, with four weeks as a cycle. At the same time, the patients were administered conventional treatments, including fluid replacement and antiemetics.

Efficacy evaluation standards [5]: Complete remission (CR): All the target lesions disappeared and lasted at least four weeks. Partial remission (PR): The product of the maximum diameter and the maximum vertical diameter of the target lesion was reduced by more than 50% for at least four weeks. Stable disease (SD): The product of the two diameters of the target lesion decreased by less than 50%, or it increased within 25% for at least four weeks. Progressive disease (PD): The product of the two diameters of the target lesion increased by ≥25% or new lesions appeared. Objective response rate (ORR) = (CR + PR)/total number of cases, Clinical benefit rate (CBR) = (CR + PR + SD)/total number of cases.

Indexes observation

Comparison of treatment effects: After 1 month of treatment, the efficacy was assessed using the evaluation criteria.

A comparison of serum VEGF-C and survivin: Four ml of venous blood was taken from each patient before and after the treatment, centrifuged at 3500 r/min for 15 min, and then the supernatant was collected. Enzyme-linked immunosorbent assays (ELISA) were used to analyze the patients' serum VEGF-C levels. The above samples were placed in a DNase and RNase-free sterile blood collection vacuum tube, and the resulting samples were centrifuged (3000 r, 20 min). Then the total serum RNA was extracted according to the Trizol reagent (produced by Shanghai Lianshuo Biotechnology Co., Ltd.). The RT-PCR method was used for amplification with 5'-CCCTGCCTGGCAGCCCTTTC-3' as the forward primer and 5'-CTGGCTCCCAGCCTTCCA-3' as the reverse primer, and a UV absorption detector was used

Table 1. Comparison of the short-term efficacy of the two groups of patients [n (%)]

Groups	n	PD	SD	PR	CR	ORR	CBR
Observation group	21	3	4	7	7	14 (66.7)	18 (85.7)
Control group	21	9	5	5	2	7 (33.3)	12 (57.1)
χ^2			4.677			4.200	
P			0.031			0.041	

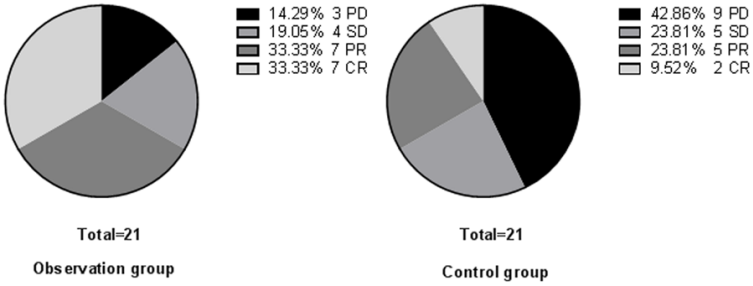

Figure 1. Comparison of the clinical efficacy between the two groups.

to determine the concentration and purity of the survivin.

Comparison of survival times between the two groups: The patients were followed up for one year, and each patient's disease aggravation and death were set as the endpoints. The overall survival times and the tumor-free survival times of the two groups were compared.

Comparison of the adverse reactions between the two groups: The gastrointestinal reactions, the platelet inhibition, and the hair loss in the two groups of patients were analyzed.

Statistical processing

SPSS 23.0 software was used for the data processing, GraphPad Prism 7.0 software was used to plot the figures. The measurement data were expressed as the mean ± standard deviation, and t-tests were performed for the comparisons between groups. The count data were expressed as (%), and chi-square tests were performed for the comparisons between groups. A difference was statistically significant when P<0.05.

Results

Comparison of the clinical efficacy between the two groups

After the treatment, in the control group, there were 2 cases of CR, 5 cases of PR, and 6 cases of SD, with ORR and CBR of 33.3% and 57.1%, respectively. In the observation group, there were 7 cases of CR, 7 cases of PR, and 4 cases of SD, with ORR and CBR of 66.7% and 85.7% respectively (P<0.05). See **Table 1** and **Figure 1**.

Comparison of the serum VEGF-C and survivin levels in the two groups

Before the treatment, the serum VEGF-C and survivin levels in the two groups had no significant differences (P> 0.05). After the treatment, apparently lower serum VEGF-C and survivin levels in the observation group were recorded, and both groups witnessed a decline in their levels (P<0.05). See **Table 2**.

Comparison of the survival times between the two groups

The overall survival times and tumor-free survival times in the observation group were (11.84±1.15) and (11.33±0.43), and in the control group they were (8.82±1.62) and (8.89±0.61). Regarding the overall survival times and tumor-free survival times, the observation group garnered a more desirable result than the control group (P<0.05). See **Table 3**.

Comparison of the adverse reactions between the two groups

In the observation group, there was one case of gastrointestinal reactions, one case of platelet inhibition, and two cases of hair loss, for a total adverse reaction rate of 19.05%. In the control group, there were two cases of gastrointestinal reactions, one case of platelet inhibition, and three cases of hair loss, for a total adverse reaction rate of 28.57%. The adverse reactions of the two groups of patients demonstrated no significant difference (χ^2=0.525, P=0.469). See **Table 4**.

Discussion

Laryngeal cancer is divided into two types: primary laryngeal cancer and secondary laryngeal

Table 2. Comparison of serum VEGF-C and survivin levels in the two groups

Groups	n	VEGF-C (ng/L)		Survivin (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	21	526.85±12.91	315.71±13.27	609.84±21.73	321.26±12.41
Control group	21	524.85±20.28	358.00±21.29	591.16±52.23	384.20±27.69
T		0.381	-7.723	1.514	-9.507
P		0.705	<0.001	0.138	<0.001

Table 3. Comparison of the survival times between the two groups of patients (months, mean ± standard error)

Groups	n	overall survival time	tumor-free survival time
Observation group	21	11.84±1.15	11.33±0.43
Control group	21	8.82±1.62	8.89±0. 61
T		6.950	15.021
P		0.031	<0.001

Table 4. Comparison of the adverse reactions between the two groups

Groups	n	Gastrointestinal reactions	Platelet inhibition	Hair loss	Adverse reaction rate
Observation group	21	1	1	2	4 (19.05)
Control group	21	2	1	3	6 (28.57)

cancer [6]. Primary laryngeal cancer refers to tumors with the primary site in the larynx, mostly squamous cell carcinoma, and secondary laryngeal cancer refers to malignant tumors in other sites, which are relatively rare in clinical practice [7]. The clinical manifestations of laryngeal cancer include hoarseness, dyspnea, coughing and dysphagia, which jeopardizes the health and life of the patients [8]. The treatments for nasopharyngeal cancer mainly include radiotherapy, chemotherapy, surgical treatment, immunotherapy, etc., among which radiotherapy is the most preferred one. The efficacy of early nasopharyngeal cancer is particularly promising, and the 5-year survival rate can reach more than 80% [9]. However, patients are, in most cases, diagnosed in the middle or late stages of nasopharyngeal cancer as a result of its rather hidden symptoms at its early stage. Moreover, it is formidable to achieve a desirable effect with radiotherapy alone [10]. Studies have found that [11], neoadjuvant chemotherapy combined with concurrent radiotherapy yields a better outcome in the treatment of advanced nasopharyngeal cancer. Neoadjuvant chemotherapy is a treatment plan that uses drugs to perform systemic chemotherapy before implementing local treatment, thereby effectively reducing tumors, with the basic efficacies of removing small lesions, eliminating distant metastasis, effectively alleviating the tumor burden, abating the clinical symptoms of patients, and enhancing the sensitivity of radiotherapy. After successfully shrinking the tumor, the further application of radiotherapy is able to reinforce the treatment effect [12]. In addition, the blood supply inside the tumor is sufficient as neoadjuvant chemotherapy avoids local fibrosis of the tumor before radiotherapy, so it is conducive to the distribution of chemotherapy drugs, thereby improving the effect of the chemotherapy [13].

Cisplatin injections are a commonly-used drug for patients with laryngeal cancer. It is a cell cycle non-specific drug, and it can inhibit the replication and proliferation of cancer cell DNA and exert a positive broad-spectrum anti-cancer effect [14]. At present, the PF regimen is commonly used in the treatment of head and neck tumors, and it has reached an effective rate of about 30%. It can effectively maintain the vocal function of the vocal cords and greatly improve patients' quality of life. However, it does not increase overall patient survival [15]. Paclitaxel is a cell cycle specific drug, that belongs to a new class of natural plant antitumor drugs. It can provide good preconditions for microtubule polymerization and effectively inhibits its depolymerization. It acts on the M phase and G2 late stage of the cell proliferation cycle and it inhibits cell mitosis, etc., thereby completely blocking the synthesis of tumor cells. In addition, the G2/M phase has the highest radiosensitivity. Paclitaxel can also block the cell cycle of cancer cells in this phase and

has a very strong radiosensitization effect [16]. At present, paclitaxel has been widely used and has become the mainstream chemotherapy regimen in clinical use in the treatment of head and neck tumors, but there is still no further decisive evidence to prove that it possesses a higher long-term survival benefit than the PF regimen [17]. The results of this study showed that the clinical efficacy of the observation group was 85.7%, which was higher than the 57.1% of the control group ($P<0.05$). The incidence of adverse reactions in the two groups was similar ($P>0.05$), which fully confirms the superiority of the TP regimen.

The analysis of the patients' serological indicators showed that the serum VEGF-C and survivin levels of the two groups of patients decreased, and of the levels in the observation group were lower than the levels in the control group. The analysis concluded that VEGF-C mainly reflects the vascular density of the patient's lesions. Some studies have pointed out [18, 19] that the invasion, metastasis and even the deterioration of the tumor cells in a patient's lesion are closely related to its blood vessel density. As the blood vessel density of the patient's lesion gradually increases, the degree of deterioration and the risk of migration also rises proportionally. The decrease of survivin gene expression in the observation group indicates that the patient's allele loss at the lesion site and the risk of tumor cell deterioration caused by gene mutations are reduced, which is of positive significance for the improvement of the patient's treatment effect. Some scholars have treated patients with albumin-bound paclitaxel combined with cisplatin injections. The patients' VEGF-C decreased, and the effect was better. The patient's therapeutic effect was negatively correlated with the survivin gene [20], which is consistent with this study. However, the following limitations were identified in this study. It was a monocentric study with a small number of participants and a short follow-up. A randomized controlled, multicenter, double-blind study with a large sample is needed to confirm this conclusion further.

In summary, albumin-bound paclitaxel combined with cisplatin injections in the treatment of laryngeal cancer can reduce the VEGF-C and survivin levels in patients, and the therapeutic effect is positive, so the combination is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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References

[1] Silva Galbiatti-Dias AL, Fernandes GMM, Castanhole-Nunes MMU, Hidalgo LF, Nascimento Filho CHV, Kawasaki-Oyama RS, Ferreira LAM, Biselli-Chicote PM, Pavarino ÉC and Goloni-Bertollo EM. Relationship between $CD44^{high}$/$CD133^{high}$/$CD117^{high}$ cancer stem cells phenotype and Cetuximab and Paclitaxel treatment response in head and neck cancer cell lines. Am J Cancer Res 2018; 8: 1633-1641.

[2] Wang J, Fan J, Gao W, Wu Y, Zhao Q, Chen B, Ding Y, Wen S, Nan X and Wang B. *LY6D* as a chemoresistance marker gene and therapeutic target for laryngeal squamous cell carcinoma. Stem Cells Dev 2020; 29: 774-785.

[3] Hoch MA, Cousins K, Nartey R, Riley K and Hartranft M. Two cases of combination therapy with cetuximab, paclitaxel, and cisplatin for advanced head and neck cancer. J Oncol Pharm Pract 2018; 24: 553-554.

[4] Guo Y, Feng Y, Cui X, Wang Q and Pan X. Autophagy inhibition induces the repolarisation of tumour-associated macrophages and enhances chemosensitivity of laryngeal cancer cells to cisplatin in mice. Cancer Immunol Immunother 2019; 68: 1909-1920.

[5] Palmieri A, Iapichino A, Cura F, Scapoli L, Carinci F, Mandrone M and Martinelli M. Pre-treatment with berberine enhances effect of 5-fluorouracil and cisplatin in HEP2 laryngeal cancer cell line. J Biol Regul Homeost Agents 2018; 32 Suppl 1: 167-177.

[6] Wei X, He J, Wang J and Wang W. MPEG-CS/Bmi-1RNAi nanoparticles synthesis and its targeted inhibition effect on $CD133^{+}$ laryngeal stem cells. J Nanosci Nanotechnol 2018; 18: 1577-1584.

[7] Tao Y, Ma C, Yin X, Fang X and Liu L. Therapeutic effects of sequential chemoradiotherapy with pemetrexed and cisplatin on locally advanced laryngeal cancer. Pak J Med Sci 2016; 32: 1126-1130.

[8] Argyris PP, Slama ZM, Ross KF, Khammanivong A and Herzberg MC. Calprotectin and the initiation and progression of head and neck cancer. J Dent Res 2018; 97: 674-682.

[9] Zhou L and Luo W. Vascular endothelial growth factor-targeted paclitaxel-loaded liposome microbubbles and inhibition of human epider-

moid-2 cell proliferation. Head Neck 2017; 39: 656-661.
[10] Tian L, Zhang J, Ren X, Liu X, Gao W, Zhang C, Sun Y and Liu M. Overexpression of miR-26b decreases the cisplatin-resistance in laryngeal cancer by targeting ATF2. Oncotarget 2017; 8: 79023-79033.
[11] Popovtzer A, Burnstein H, Stemmer S, Limon D, Hili O, Bachar G, Sopov V, Feinmesser R, Groshar D and Shvero J. Phase II organ-preservation trial: concurrent cisplatin and radiotherapy for advanced laryngeal cancer after response to docetaxel, cisplatin, and 5-fluorouracil-based induction chemotherapy. Head Neck 2017; 39: 227-233.
[12] Jiang Q, Liu S, Hou L, Guan Y, Yang S and Luo Z. The implication of LncRNA MALAT1 in promoting chemo-resistance of laryngeal squamous cell carcinoma cells. J Clin Lab Anal 2020; 34: e23116.
[13] Vossen DM, Verhagen CVM, Verheij M, Wessels LFA, Vens C and van den Brekel MWM. Comparative genomic analysis of oral versus laryngeal and pharyngeal cancer. Oral Oncol 2018; 81: 35-44.
[14] Dietz A, Wichmann G, Kuhnt T, Pfreundner L, Hagen R, Scheich M, Kölbl O, Hautmann MG, Strutz J, Schreiber F, Bockmühl U, Schilling V, Feyer P, de Wit M, Maschmeyer G, Jungehülsing M, Schroeder U, Wollenberg B, Sittel C, Münter M, Lenarz T, Klussmann JP, Guntinas-Lichius O, Rudack C, Eich HT, Foerg T, Preyer S, Westhofen M, Welkoborsky HJ, Esser D, Thurnher D, Remmert S, Sudhoff H, Görner M, Bünzel J, Budach V, Held S, Knödler M, Lordick F, Wiegand S, Vogel K, Boehm A, Flentje M and Keilholz U. Induction chemotherapy (IC) followed by radiotherapy (RT) versus cetuximab plus IC and RT in advanced laryngeal/hypopharyngeal cancer resectable only by total laryngectomy-final results of the larynx organ preservation trial DeLOS-II. Ann Oncol 2018; 29: 2105-2114.
[15] Rocha GZ, Dias MM, Ropelle ER, Osório-Costa F, Rossato FA, Vercesi AE, Saad MJ and Carvalheira JB. Metformin amplifies chemotherapy-induced AMPK activation and antitumoral growth. Clin Cancer Res 2011; 17: 3993-4005.
[16] Matoba T, Ijichi K, Yanagi T, Kabaya K, Kawakita D, Beppu S, Torii J and Murakami S. Chemoselection with docetaxel, cisplatin and 5-fluorouracil (TPF) regimen followed by radiation therapy or surgery for pharyngeal and laryngeal carcinoma. Jpn J Clin Oncol 2017; 47: 1031-1037.
[17] Xiang M, Colevas AD, Holsinger FC, Le QX and Beadle BM. Survival after definitive chemoradiotherapy with concurrent cisplatin or carboplatin for head and neck cancer. J Natl Compr Canc Netw 2019; 17: 1065-1073.
[18] Yabe S, Iwamoto N, Inokuchi T, Nara M, Saita C, Onishi M, Goto R, Yonekura R, Ishiba T, Honda Y, Miyamoto H and Aruga T. A case report on the effectiveness of olaparib in a patient with recurrent breast cancer with human immunodeficiency virus infection. Gan To Kagaku Ryoho 2020; 47: 1089-1092.
[19] Lv X, Song DM, Niu YH and Wang BS. Inhibition of heme oxygenase-1 enhances the chemosensitivity of laryngeal squamous cell cancer Hep-2 cells to cisplatin. Apoptosis 2016; 21: 489-501.
[20] Hashimoto M, Shirakawa Y, Maeda N, Tanabe S, Noma K, Sakurama K, Katsui K, Nishizaki M and Fujiwara T. Induction chemoradiotherapy including docetaxel, cisplatin, and 5-fluorouracil for locally advanced esophageal cancer. Esophagus 2020; 17: 127-134.