Am J Transl Res 2021;13(6):7394-7399
www.ajtr.org /ISSN:1943-8141/AJTR0130353

Original Article

The efficacy of cisplatin and low-temperature plasma radiofrequency ablation in advanced laryngeal cancer patients and on the serum survivin levels

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Received January 18, 2021; Accepted February 9, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Objective: To investigate the effect of cisplatin injections combined with low-temperature plasma radiofrequency ablation on the clinical efficacy and serum survivin levels in advanced laryngeal cancer patients. Methods: A total of 42 patients with locally advanced laryngeal cancer treated in our hospital from January 2018 to June 2020 were recruited as the study cohort and placed in a control group (21 cases) or a treatment group (21 cases) according to the medication administered to each patient. The patients in the control group were treated with CO_2 laser resections under laryngoscopy combined with cisplatin injections, and the patients in the observation group were treated with low-temperature plasma radiofrequency ablation combined with cisplatin injections. The clinical efficacies in the two groups were observed and the WHOQOL-BREF scores, tumor marker levels, and serum survivin levels were compared. Results: After the treatment, the ORR and CBR in the control group were 33.3% and 61.9%, respectively, levels that were significantly lower than the 66.7% and 90.5% in the observation group ($P<0.05$). The observation group's physiological, psychological, and social relations dimension scores were significantly higher than the corresponding scores in the control group ($P<0.05$). The tumor markers in the observation group were significantly lower in the serum CA72-4, CA19-9, and SCC-Ag levels than they were in the control group ($P<0.05$). The observation group exhibited lower serum survivin levels than the control group ($P<0.05$). Conclusion Cisplatin injections combined with low-temperature plasma radiofrequency ablation has a significant effect on the treatment of locally advanced laryngeal cancer. It can improve patients' quality of life, reduce the tumor marker levels in the body, and inhibit the serum survivin levels.

Keywords: Low-temperature plasma radiofrequency ablation, laryngeal tumors, chemotherapy, curative effect, survivin

Introduction

Laryngeal cancer is a common malignant tumor of the head and neck. About 40% of the patients who see a doctor for the first time for this condition are in the middle and advanced stages of the disease. Nevertheless, for patients in the early stages of laryngeal cancer, surgery is often successful, but for patients in the advanced stages, surgery alone cannot achieve satisfactory results. The chief option for locally-advanced laryngeal cancer is concurrent radiotherapy and chemotherapy [1, 2]. Using new and improved chemotherapeutic methods, the therapeutic effects of chemotherapy on head and neck tumors, especially advanced tumors, have gradually gained more attention [3]. The cisplatin-based TPF (docetaxel, cisplatin, fluorouracil) chemotherapy regimen is a new regimen for laryngeal cancer and hypopharyngeal cancer, and its efficacy has also been widely recognized [4]. Low-temperature plasma radiofrequency ablation is an emerging surgical technique, and it involves less intraoperative blood loss and a clearer surgical vision [5]. Survivin, a new member of the intracellular apoptosis inhibitor protein (IAPs) family, is abnormally up-expressed in the serum of patients with malignant tumors [6]. We therefore aimed to explore the effects of cisplatin injections combined with low-temperature plasma radiofrequency ablation on the serum sur-

vivin levels in advanced laryngeal cancer patients, and to provide a scientific basis for the clinical treatment.

Materials and methods

Participants

42 patients with locally advanced laryngeal cancer treated in our hospital from January 2018 to June 2020 were enrolled in this study, including 22 males and 20 females ranging in age from 43 to 74 (60.27±1.57) years old. The patients were placed into the control group (21 cases) or the observation group (21 cases) according to the medication administered to each patient. In the control group, there were 10 males and 11 females, and they ranged in age from 43-74 (61.15±1.83) years old. In the observation group, there were 12 males and 9 females, and they ranged in age from 44-73 (60.19±1.81) years old. We observed no significant differences in the two groups' general information.

Inclusion criteria [7]: (1) All the patients met the diagnostic criteria for locally advanced laryngeal cancer. (2) All the patients were confirmed to have laryngeal squamous cell carcinoma through a biopsy and a pathological examination. (3) All the participants provided a signed informed consent form.

Exclusion criteria: (1) Patients with severe liver or kidney dysfunction. (2) Patients with consciousness disorders or mental illnesses. (3) Patients with other malignant tumors. (4) Patients allergic to the drugs used in the study. (5) Patients who were undergoing chemotherapy or other treatments. (6) Patients with incomplete clinical data. (7) Patients also suffering from severe infections or gastrointestinal bleeding. (8) Patients who did not provided an informed consent. This study was approved by our hospital's ethics committee.

Research methods

The patients in the observation group were treated with low-temperature plasma radiofrequency ablation combined with cisplatin injections, and the patients in the control group were treated laryngoscopically with CO_2 laser resections combined with cisplatin injections.

(1) Cisplatin injection treatment: After the operation, the patients underwent a 75 mg/m^2 intravenous infusion of docetaxel for more than 30 min on the first day. Cisplatin injections (Yunnan Gejiu Biopharmaceutical Co., Ltd.) were used on days 1 to 3 at 25 mg/ml, once a week, for 4 weeks as a course of treatment. The treatment lasted for one course.

(2) Low-temperature plasma radiofrequency ablation: We performed general anesthesia after intubating the patients. The patients assumed a supine position, and we inserted the American Arthrocare II plasma radiofrequency instrument into the patient's mouth to fully expose the glottis. We used endoscopy to check the patient's glottis, and adjusted the radiofrequency of the ablation and hemostasis appropriately. Then we lifted the patient's glottic tumor in the middle with one hand, and used the other hand to remove the tumor and glottic lesions with the low-temperature plasma. The resection range was set at 5 mm from the outer edge of the patient's lesion base. We then sent the basal tissue immediately for a pathological examination after the patient's tumor was removed. If it tested negative, the operation ended. If it tested positive, the patient's basal tissue was removed. We advised the patients not to speak for 15 days after the operation. CO_2 laser resection: We used CO_2 laser resection to remove the tumor tissue. The other surgical procedures were the same as above.

Efficacy evaluation criteria

Complete remission (CR): All the target lesions disappeared for at least 4 weeks. Partial remission (PR): The product of the maximum diameter and maximum vertical diameter of the target lesion decreased by more than 50% for at least 4 weeks. Stable disease (SD): The product of the two diameters of the target lesion was reduced by less than 50%, or it was increased by less than 25% for at least 4 weeks. Progressive disease (PD): The product of the two diameters of the target lesion increased by ≥25% or new lesions occurred. Objective response rate (ORR) = (CR + PR)/total number of cases; Clinical benefit rate (CBR) = (CR + PR + SD)/total number of cases.

Observation indicators

Quality of life: The World Health Organization Quality of Life Brief (WHOQOL-BREF) was used to assess the patients' quality of life. The scale

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

Group	n	PD	SD	PR	CR	ORR	CBR
observation group	21	2	5	7	7	14 (66.7)	19 (90.5)
control group	21	8	6	5	2	7 (33.3)	13 (61.9)
X^2						4.677	4.725
P						0.031	0.03

includes 26 routine assessment questions and 3 additional questions covering the physiological, psychological, and social relations dimensions, each worth 100 points. The higher the score, the better the quality of life.

Tumor markers and the serum survivin expressions 5 mL of fasting venous blood was collected, centrifuged at 3000 r/min for 5 min, separated and stored at -70°C. The carbohydrate antigen 72-4 (CA72-4, Shanghai Jing Anti-Bioengineering Co., Ltd.), carbohydrate antigen 19-9 (CA19-9, Shanghai Huzhen Biotechnology Co., Ltd.), squamous cell carcinoma-associated antigen (SCC-Ag, and Wuhan Boshikang Bioengineering Co., Ltd.) levels were determined using chemiluminescence immunoassays. The survivin content was determined using the ELISA method. All the operations were carried out in strict accordance with the instructions.

Adverse reactions

The adverse reactions were assessed with reference to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Statistical methods

The measurement data were expressed as the mean ± standard deviation, and for the comparisons t tests were performed. The enumeration data were given as (%), and the comparisons between groups were performed using χ^2 tests. Significance was set at P<0.05. All the analyses were carried out using SPSS software (version 23, SPSS, Inc., Chicago, IL, USA).

Results

Clinical efficacy

The control group had 2 cases of CR, 5 cases of PR, and 6 cases of SD, with ORR and CBR of 33.3% and 61.9%, respectively. The observation group had 7 cases of CR, 7 cases of PR, and 5 cases of SD, with ORR and CBR of 66.7% and 90.5% respectively. Significant differences were observed in ORR and CBR between the two groups (P<0.05), see **Table 1**.

The WHOQOL-BREF scores

We measured no significant differences in the WHOQOL-BREF scores in the two groups prior to the treatment (P>0.05). The physiological, psychological, and social relationship dimensions post-treatment scores in the observation group were remarkably higher compared to the control group (P<0.05, **Table 2**).

Serum index

Regarding the post-treatment serum survivin levels, the observation group had a lower level than the control group (P<0.05, **Table 2**).

Tumor marker levels

We examined the tumor marker levels prior to the treatment, and no statistical differences were shown between the two groups (P>0.05). After the treatment, the CA72-4, CA19-9, and SCC-Ag tumor markers in the observation group had lower levels compared to the control group (P<0.05). See **Table 3**.

Adverse events

Concerning the toxic side effects, no bone marrow suppression, thrombocytopenia, or leukopenia occurred. However, the control group had 3 cases of nausea and vomiting, 4 cases of diarrhea, for an adverse reaction rate of 33.3%. The observation group had 1 case of nausea and 2 cases of diarrhea, for an adverse reaction rate of 19.0%. No significant differences were observed between the two groups (χ^2 =1.109, P=0.292). See **Table 4**.

Discussion

Laryngeal cancer can be classified into primary laryngeal cancer and secondary laryngeal cancer [8]. Primary laryngeal cancer refers to a tumor whose primary site is located in the larynx, chiefly squamous cell carcinoma, and secondary laryngeal cancer is defined as malignant tumors originating from other sites and are relatively rare in clinical practice [9]. The

Table 2. Comparison of the quality of life scores and serum index levels of the two groups of patients before and after the treatment

Index	Time	observation group (n=21)	control group (n=21)	t	P
physiological dimension	before treatment	41.53±3.03	39.90±3.38	1.641	0.109
	after treatment	73.05±2.04	52.85±5.02	17.06	<0.01
psychological dimension	before treatment	37.69±2.22	38.60±3.37	1.034	0.307
	after treatment	71.45±2.04	51.88±3.68	21.292	0.001
social dimension	before treatment	38.07±2.28	38.76±3.83	0.709	0.482
	after treatment	69.67±2.29	49.63±3.08	23.914	<0.01
Survivin (pg/mL)	before treatment	619.87±27.25	609.87±46.28	0.853	0.399
	after treatment	331.00±16.42	396.80±27.17	9.498	<0.01

Table 3. Comparison of the tumor marker levels between the two groups

Index	Time	observation group (n=21)	control group (n=21)	t	P
CA72-4/(U·mL^{-1})	before treatment	13.77±0.54	14.17±1.14	1.641	0.109
	after treatment	7.75±0.48	10.89±1.29	10.418	<0.01
CA19-9/(U·mL^{-1})	before treatment	21.71±1.83	20.04±3.58	1.908	0.064
	after treatment	14.53±2.10	18.27±2.83	4.849	<0.01
SCC-Ag/(ng·mL^{-1})	before treatment	2.95±0.01	2.94±0.02	1.279	0.208
	after treatment	1.51±0.13	2.03±0.02	17.106	<0.01

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

group	n	nausea and vomiting	diarrhea	rate of adverse reaction
observation group	21	3	4	7 (33.3)
control group	21	2	2	4 (19.0)

clinical manifestations include hoarseness, dyspnea, coughing, and dysphagia, and they have an extremely negative impact on the health and life of the patient. Unfortunately, due to a lack of specificity in the early clinical symptoms, most patients are already in the middle and late stages once diagnosed, missing the optimal treatment time [10]. The surgical option is a commonly used treatment for patients with laryngeal cancer, and it can remove the lesioned tissue and prolong the life of the patient. Nevertheless, because of the risk and the nature of the trauma, the integrity of the laryngeal structure is prone to be damaged, leading some patients to lose their laryngeal function after their surgery [11].

Laryngeal cancer is not extremely sensitive to radiotherapy, and the integrity of the larynx and the voice function thus can be preserved greatly and the quality of life can be improved. It is possible for patients to undergo a second surgical treatment even if the disease recurs after the radiotherapy [12]. Scholars reported [13] that concurrent radiotherapy and chemotherapy are more efficient than radical radiotherapy alone, yet the treatment is characterized by a higher incidence of adverse drug reactions as well. Taken together, strengthening the chemotherapy for patients with laryngeal cancer is of pivotal significance for patient prognosis.

Cisplatin injections are a mainstay 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 good broad-spectrum anti-cancer effect. In the meantime, adverse events such as nausea, vomiting, hair loss, and leukemia are also frequently documented, resulting in a poor treatment compliance and poor patient cooperation [14]. Additionally, with the constant advances in surgical techniques, low-temperature plasma radiofrequency ablation has been widely used in the clinical treatment of patients with laryngeal cancer [15]. Compared with ordinary surgical methods, it can cut the soft tissue of the patient at a lower temperature (40-70°C),

and at the same time, the strong suction and hemostatic function can reduce the tissue damage during the operation [16]. Moreover, no thermal tissue damage occurs, the wound heals faster, and clinical complications such as infections and pharyngeal fistulas can easily occur due to less carbonization and smog during the operation. It can be deduced that compared with ordinary surgery, low-temperature plasma radiofrequency ablation surgery can positively protect the patient's laryngeal mucosa. This study showed that after treatment, the ORR and CBR of the control group and the observation group were 33.3%, 61.9% and 66.7%, 90.5% respectively (P<0.05), and the WHOQOL-BREF scores of the two groups increased significantly (P<0.05), but the increase was more significant in the observation group (P<0.05). And the incidences of adverse reactions in the two groups showed no significant difference. We found that cisplatin combined with low-temperature plasma radiofrequency ablation is effective at treating locally-advanced laryngeal cancer.

It is well known that CA19-9 and CA72-4 are tumor-related proteins, and they are used as an index to diagnose digestive system tumors. However, in recent years, it has been found that these two proteins have significantly higher levels in the serum of laryngeal cancer patients when compared to healthy people [17]. SCC-Ag is a human squamous cell carcinoma-related antigen, and its specific expression is related to malignant tumors derived from squamous epithelial cells [18]. In this study, the CA72-4, CA19-9, and SCC-Ag levels of the tumor markers in the observation group post-treatment revealed a markedly lower level compared to the control (P<0.05), suggesting that cisplatin injections combined with low-temperature plasma radiofrequency ablation can reduce the tumor marker levels in patients with locally-advanced laryngeal cancer.

Survivin is a new member of the apoptosis inhibitor protein family and has been proved to be the strongest apoptotic inhibitor currently known. It participates in angiogenesis and cell cycle regulation, and it regulates tumor cell division, promotes tissue blood vessel formation, and inhibits cell apoptosis as well. Importantly, it can inhibit the apoptosis induced by Fas, caspase, bax and certain chemotherapeutic drugs. Through cell cycle-dependent expression, it can resist the induction of apoptosis in the G2/M phase. Its overexpression can prevent cell apoptosis, thereby losing the restriction of apoptosis, and eventually forming an abnormal proliferation of tissue cells [19, 20].

Here we reported that the serum survivin level in the observation group was significantly lower compared to the control group (P<0.05), suggesting that the changes in the survivin expressions before and after the treatment may provide a new basis for assessing the prognosis of laryngeal cancer, and it is expected to become a new molecular marker for the diagnosis and treatment of laryngeal cancer and provide a basis for future targeted therapy. However, this study failed to determine whether the serum CA72-4, CA19-9, and SCC-Ag expression levels are independent risk factors for laryngeal cancer patients. In the future, further trials will be carried out to clarify this.

In summary, cisplatin injections combined with low-temperature plasma radiofrequency ablation for the treatment of locally advanced laryngeal cancer can generate a relatively ideal outcome, and the treatment can improve patients' quality of life, reduce the tumor marker levels in the body, and inhibit the serum survivin levels.

Disclosure of conflict of interest

None.

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