JBUON 2020; 25(4): 1976-1981
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Efficacy of nedaplatin combined with docetaxel in patients with nasopharyngeal carcinoma and its influence on ECRG4 and VEGF expressions

Dongzhi Zuo, Guancheng Liu, Ming Deng, Yanyong Gao

Department of Otolaryngology Head and Neck Surgery, affiliated Hospital of Guilin Medical University, Guilin, China.

Summary

Purpose: *To explore the efficacy of nedaplatin combined with docetaxel in patients with nasopharyngeal carcinoma and its influence on the expressions of esophageal cancer-related gene 4 (ECRG4) and vascular endothelial growth factor (VEGF).*

Methods: *86 patients with nasopharyngeal carcinoma, admitted to and treated in our hospital from March 2016 to February 2018, were selected and randomly divided into control group (n=43) and observation group (n=43). Chemotherapy combining cisplatin with fluorouracil was administered in the control group, while nedaplatin combined with docetaxel was given in the observation group. Then the efficacy, adverse reactions, the levels of serum hypoxia-inducible factor-1a (HIF-1a) and VEGF in patients before and after treatment, and the change in the expression level of ECRG4 in foci after treatment were compared between the two groups. After 1-year follow-up, the improvement in quality of life was compared between the two groups of patients.*

Results: *The objective remission rate and disease control rate in the observation group were obviously higher than in the control group ($p<0.05$), and the total incidence rate of adverse reactions in the observation group was evidently lower than in the control group ($p<0.05$). At 2, 4, and 6 weeks after treatment, the two groups of patients had substantially decreased levels of serum HIF-1a and VEGF, and the declines were more apparent in the observation group ($p<0.05$). The expression level of ECRG4 in foci in the observation group was remarkably higher than in the control group ($p<0.05$). The observation group exhibited more apparent improvement in quality of life than the control group ($p<0.05$).*

Conclusions: *Nedaplatin combined with docetaxel has better short-term efficacy in nasopharyngeal carcinoma, with milder adverse reactions, and it can reduce the levels of serum HIF-1a and VEGF, and up-regulate ECRG4 expression in patients, exerting an anti-carcinoma effect.*

Key words: *nedaplatin, docetaxel, nasopharyngeal carcinoma, ECRG4, VEGF*

Introduction

Nasopharyngeal carcinoma, a clinically common malignancy, originates from nasopharyngeal mucosa and belongs to squamous cell carcinoma. The main clinical manifestations of nasopharyngeal carcinoma include nosebleeding, rhinobyon, headache, tinnitus and swollen lymph nodes [1]. The clinical treatment of nasopharyngeal carcinoma is dominated by radiotherapy that can effectively kill nasopharyngeal carcinoma cells, with significant efficacy [2]. However, nasopharyngeal carcinoma is highly insidious at the early stage, and once definitely diagnosed, it is frequently at middle-advanced stages when the efficacy of radiotherapy is far from satisfactory. This malignancy is prone to local recurrence, so chemotherapy needs to be also administered [3]. Esophageal can-

Corresponding author: Yanyong Gao, MM. Department of Otolaryngology Head and Neck Surgery, affiliated Hospital of Guilin Medical University, No.15, Lequn Rd, Xiufeng District, Guilin, 541001 Guangxi, China.
Tel: +86 013635189180, Email: doctorgaogl@163.com
Received: 10/02/2020; Accepted: 16/03/2020

cer-related gene 4 (ECRG4) is a potential tumor suppressor gene, and its inactivation and changes are associated with the development of various malignancies [4]. Vascular endothelial growth factor (VEGF) can play an important role in the development and progression of nasopharyngeal carcinoma [5]. The patients in the present study were administered nedaplatin combined with docetaxel and the influence on ECRG4 and VEGF expressions were analyzed, hoping to provide bases for the treatment of this disease.

Methods

General information

A total of 86 nasopharygeal carcinoma patients admitted to and treated in our hospital from March 2016 to February 2018 were enrolled and assigned into a control group (n=43) and observation group (n=43) using a random number table. Inclusion criteria: 1) patients conforming to the diagnostic criteria for nasopharyngeal carcinoma [6]; 2) those with predicted survival >3 months; and 3) those agreeing to sign the informed consent. Exclusion criteria: 1) patients complicated with other cancers; 2) those with mental diseases; or 3) those who had severe allergies to the drugs used in the present study. The differences between the two groups were not statistically significant (p>0.05) (Table 1). This study was approved by the Ethics Committee of our hospital. Signed informed consents were obtained from all participants before the study entry.

Treatment methods

All patients received routine radiotherapy. They were first instructed to lie in supine position, and the body contour, tumor area, clinical target and planning target were delineated through CT scanning for radiotherapy at the dose of 20 Gy/time once per day and 5 times every week for 6 weeks, with a total dose of 60.0 Gy. From the 1st day of radiotherapy, cisplatin combined with fluorouracil was administered in the control group as follows: 30 min prior to treatment, 10 mg of dexamethasone was given through intravenous bolus, and then cisplatin was intravenously instilled at a dose of 100 mg/m^2. From the 1st to 5th day, fluorouracil was intravenously instilled at a dose of 500 mg/m^2 for 6 weeks. In the observation group, nedaplatin combined with docetaxel were given as follows: nedaplatin and docetaxel were simultaneously intravenously instilled at a dose of 80 mg/m^2 and 40 mg/m^2, respectively, once a week for 6 weeks.

Detection of relevant indicators

Before and after treatment, 5 mL of fasting venous blood was collected from the two groups of patients to extract serum. Then the levels of serum hypoxia-inducible factor-1α (HIF-1α) and VEGF were determined using enzyme-linked immunosorbent assay (ELISA) strictly according to the instructions of the related kits. An appropriate number of focal tissues were taken under an endoscope before and after treatment, and ribonucleic acids (RNAs) were isolated from the foci and reversely transcribed into complementary deoxyribonucleic acids (cDNAs) using RNA extraction kit and cDNA synthesis kit, respectively. Then cDNAs were amplified using polymerase chain reaction (PCR) kit. Finally, the messenger RNA (mRNA) expression level of ECRG4 was calculated based on the amplification curve.

Observation indicators

The short-term response of patients was evaluated based on the Response Evaluation Criteria in Solid Tumors [7]: 1) complete remission (CR): all visible foci disappear, which lasts for ≥4 weeks; 2) partial remission (PR): the maximum diameter of tumors is reduced by ≥50%, which lasts for ≥4 weeks; 3) stable disease (SD): non-CR and non-PR; 4) progressive disease (PD): the sum of diameters of target foci is increased by ≥20%, and the absolute of the diameter sum is increased by ≥5 mm, with new foci appear. The incidence rate of adverse reactions, including thrombocytopenia, reduction in neutrophils, hepatic dysfunction and gastrointestinal reaction, were compared between the two groups of patients.

Table 1. Comparison of baseline information between the two groups of patients

Item	*Control group (n=43)*	*Observation group (n=43)*	t/x^2	*p*
Age, years	48-79	45-75	-	-
Mean, years	54.26±7.21	54.38±7.96	0.109	0.457
Male/female (n)	29/14	31/12	0.055	0.814
Histology, n (%)				
Squamous carcinoma	37 (86.05)	38 (88.37)	0.347	0.987
Adenocarcinoma	2 (4.65)	1 (2.33)		
Squamous adenocarcinoma	3 (6.98)	3 (6.98)		
Undifferentiated carcinoma	1 (2.33)	1 (2.33)		
Clinical stage, n (%)				
Stage I-II	11 (25.58)	14 (32.56)	0.226	0.635
Stage III-IV	32 (74.42)	29 (77.44)		

Statistics

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was employed for data processing. Measurement data were expressed as (x±s) and subjected to t-test. Enumeration data were presented as percents and analyzed using x^2 test. The survival curves were platted using the Kaplan-Meier method and log-rank test was used to compare survival between groups. P<0.05 suggested statistically significant difference.

Results

Efficacy in the two groups

The total remission rate in the observation group was obviously higher than in the control group (p<0.05) (Table 2).

Adverse reactions in the two groups

The total incidence rate of adverse reactions in the observation group was evidently lower than that in the control group (p<0.05) (Table 3).

Changes in serum HIF-1a and VEGF expressions in patients after treatment

At 2, 4 and 6 weeks after treatment, the levels of serum HIF-1α and VEGF were remarkably lowered in the two groups of patients, and the declines were more obvious in the observation group (p<0.05) (Tables 4 & 5).

ECRG4 expression in focal tissues in the two groups of patients before and after treatment

At 6 weeks after treatment, the expression of ECRG4 was up-regulated in the two groups of patients, and was markedly higher in the observation group than that in the control group (p<0.05) (Table 6).

Quality of life of patients in both groups

The patients in the observation group had markedly higher social function, cognitive function, emotional function, role function, physical function and overall health status scores than those in the control group (p<0.05) (Table 7).

Discussion

Nasopharyngeal carcinoma is a highly malignant tumor in the head and neck and belongs to squamous cell carcinoma originating from epithelial cells. Its morbidity rate varies significantly from place to place and is substantially higher in Asia and Africa than in Europe and America [8]. Nasopharyngeal carcinoma is induced by many

Table 2. Comparison of efficacy between the two groups of patients

Group	*PD*	*SD*	*PR*	*CR*	*Total remission rate*
Observation group, n (%)	3 (6.98)	6 (13.95)	24 (55.81)	10 (23.26)	34 (79.07)
Control group, n (%)	10 (23.26)	17 (39.53)	13 (30.23)	3 (6.98)	16 (37.21)
x^2	13.808				
p	<0.001				

Table 3. Adverse reactions in the two groups

Group	*n*	*Gastrointestinal discomfort*	*Oral mucositis*	*Hypersensitivity*	*Total incidence rate*
Observation group, n (%)	43	3 (6.98)	2 (4.65)	1 (2.33)	6 (13.95)
Control group, n (%)	43	7 (16.28)	4 (9.30)	5 (11.63)	16 (37.21)
x^2					4.947
p					0.026

Table 4. Comparison of HIF-1α level between the two groups of patients before and after treatment (ng/L)

Group	*n*	*Before treatment*	*2 weeks after treatment*	*4 weeks after treatment*	*6 weeks after treatment*
Observation group	43	17.82±3.13	10.25±2.64*	6.73±1.34*	3.16±0.67*
Control group	43	17.24±3.18	13.17±2.68*	12.09±1.87*	10.02±0.89*
t		0.074	31.053	34.106	28.157
p		0.814	<0.001	<0.001	<0.001

*p<0.05 *vs.* before treatment.

Table 5. Comparison of VEGF level between the two groups of patients before and after treatment (mg/L)

Group	n	Before treatment	2 weeks after treatment	4 weeks after treatment	6 weeks after treatment
Observation group	43	265.83±9.85	201.06±8.32*	181.63±7.86*	138.36±6.42*
Control group	43	266.76±9.75	238.65±8.67*	203.52±8.15*	185.75±7.18*
t		0.178	19.147	28.166	24.357
p		0.865	<0.001	<0.001	<0.001

*p<0.05 *vs.* before treatment.

Table 6. Comparison of ECRG4 mRNA expression level between the two groups before and after treatment

Group	n	Before treatment	6 weeks after treatment	t	p
Observation group	43	0.65±0.07	2.02±0.15	18.673	<0.001
Control group	43	0.62±0.06	1.04±0.09	14.562	<0.001
t		0.075	19.053		
p		0.815	<0.001		

Table 7. Comparison of quality of life score between the two groups of patients after treatment

Item	*Control group*	*Observation group*	*t*	*p*
Social function	30.76±3.15	41.64±3.23	18.677	<0.001
Cognitive function	60.68±3.36	73.52±3.69	19.688	<0.001
Emotional function	56.54±3.89	70.13±3.06	26.006	<0.001
Role function	30.69±3.45	40.47±3.57	16.801	<0.001
Physical function	62.48±3.25	69.36±3.57	18.325	<0.001
Overall health status	57.37±3.59	68.52±2.61	22.720	<0.001

factors, including smoking, excessive drinking, Epstein-Barr (EB) virus infection, diet, heredity and environment [9,10]. Nasopharyngeal carcinoma, once definitely diagnosed, tends to be at middle-advanced stages, so it is difficult to be radically cured by means of surgery and prone to recurrence [11]. Since nasopharyngeal carcinoma is relatively sensitive to x-rays, radiotherapy is often performed, but its efficacy is not satisfactory in advanced-stage patients. Thus, combined with chemotherapy is warranted to extend the patient survival [12].

Radiotherapy can be employed to pinpoint tumor foci, thereby effectively inhibiting the proliferation of tumor cells, and it has become the main clinical treatment method of nasopharyngeal carcinoma [13]. Chemotherapy is an important anti-tumor treatment. In particular, its efficacy is more notable in the patients at middle-advanced stages, but more toxic side effects and low patient compliance negatively impact the long-term efficacy of chemotherapy [14]. According to the results of this study, the total remission rate of patients after radiotherapy in the observation group was obviously higher than that in the control group (79.07% *vs.* 37.21%), and the total incidence rate of adverse reactions in patients in the observation group was evidently lower than that in the control group (p<0.05). The reason is that with the development of modern imaging technology, foci can be accurately delineated, thereby improving the efficacy of diagnosis. Docetaxel, a taxol derivative, can significantly inhibit the proliferation of tumor cells and effectively kill tumor cells, while with an obviously sensitizing effect on radiation, it enhances the induction of tumor cell apoptosis by x-rays [15]. Nedaplatin is a new-generation platinum compound that can be combined with water to form multiple ionic substances, thereby inhibiting DNA replication and resisting tumors. Besides, it has obviously fewer toxic side effects and 10-fold higher water-solubility than cisplatin [16], so nedaplatin treatment can be successfully completed without massive hydration, and patients exhibit high compliance and more notable long-term response.

HIF-1 is a pivotal transcription factor that can be expressed in tumor cells and comprises two subunits HIF-1β and HIF-1α [17]. Of them, HIF-1α, as the major functional unit of HIF-1, can control the activity of HIF-1 pathway, and the up-regulation of its expression will enhance the proliferation of tumor cells, aggravating the disease in patients [18]. VEGF, a strongly specific angiogenic growth factor,

plays a vital role in tumor neovascularization, and activates endothelial cells to secrete large numbers of proteolytic enzymes, thereby degrading matrix membranes, weakening the barrier effect and promoting constant progression and deterioration of tumors. Meanwhile, it can accelerate the adhesion and dislocation of endothelial cells and passes through vascular matrices to intersect with the vascular system in tumor tissues, providing adequate nutrients for the rapid growth of tumor cells [19]. The results of this study showed that the levels of serum HIF-1α and VEGF were notably decreased in the two groups of patients at 2, 4 and 6 weeks after treatment, and the decreases were greater in the observation group ($p<0.05$), because nedaplatin combined with docetaxel can not only enhance the effect of radiotherapy, promote tubulin polymerization in a short time, and inhibit tubulin depolymerization and endothelial cell proliferation, exerting an anti-angiogenic effect, and ultimately lowering VEGF expression, but also intensify reoxygenation in tumor cells to weaken HIF-1α activity and down-regulate its expression, thereby inhibiting tumor cell proliferation.

ECRG4, one of the Calpain family members, is expressed in most tissues in human body to a certain extent, and it is crucial for the stable activity of Calpain1 and Calpain2 and closely associated with the development and progression of tumors [20]. The results of this study revealed that the expression of ECRG4 in focal tissues was elevated in the two groups of patients at 6 weeks after treatment, and considerably higher in the observation group than in the control group ($p<0.05$), implying that the administration of nedaplatin combined with docetaxel based on radiotherapy in patients can substantially up-regulate ECRG4 expression to repress the proliferation, cloning and infiltration of nasopharyngeal carcinoma cells, and induce tumor cell apoptosis, thus benefiting the prognosis of patients, and improving their quality of life.

Conclusions

In conclusion, the administration of nedaplatin combined with docetaxel in nasopharyngeal carcinoma patients can enhance the efficacy of radiotherapy as well as up-regulate the expressions of ECRG4 and VEGF, and reduce toxic side effects, thereby improving the quality of life of patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. Bian S, Wang Z, Chen Y, Li R. SPLUNC1 and MLL3 regulate cancer stem cells in nasopharyngeal carcinoma. JBUON 2019;24:1700-05.
2. Kang M, Zhou P, Long J et al. A new staging system for nasopharyngeal carcinoma based on intensity-modulated radiation therapy (IMRT). Oncotarget 2017;8:94188-96.
3. Chen J, Lu F, Hu C. MicroRNA-299 targets VEGFA and inhibits the growth, chemosensitivity and invasion of human nasopharyngeal carcinoma cells. JBUON 2019;24:2049-55.
4. Moriguchi T, Takeda S, Iwashita et al. Ecrg4 peptide is the ligand of multiple scavenger receptors. Sci Rep 2018;8:4048.
5. Lawicki S, Zajkowska M, Glazewska EK, Bedkowska GE, Szmitkowski M. Plasma levels and diagnostic utility of VEGF, MMP-2 and TIMP-2 in the diagnostics of breast cancer patients. Biomarkers 2017;22:157-64.
6. Wei F, Tang L, He Y et al. BPIFB1 (LPLUNC1) inhibits radioresistance in nasopharyngeal carcinoma by inhibiting VTN expression. Cell Death Dis 2018;9:432.
7. Dang YZ, Li X, Huang SG et al. Curative effect of stereotactic body radiotherapy for unresectable massive primary liver cancer. Mol Clin Oncol 2017;6:911-6.
8. Huang D, Song SJ, Wu ZZ et al. Epstein-Barr Virus-Induced VEGF and GM-CSF Drive Nasopharyngeal Carcinoma Metastasis via Recruitment and Activation of Macrophages. Cancer Res 2017;77:3591-3604.
9. Christodoulopoulos N, Mastronikolis N, Tsiambas E et al. Impact of different therapeutic regimens on survival of patients with nasopharyngeal carcinoma. JBUON 2019;24:2418-S22.
10. Yao JJ, Yu XL, Zhang F et al. Radiotherapy with neoadjuvant chemotherapy versus concurrent chemoradiotherapy for ascending-type nasopharyngeal carcinoma: a retrospective comparison of toxicity and prognosis. Chin J Cancer 2017;36:26.
11. Chen X, Li J, Li CL, Lu X. Long non-coding RNA ZFAS1 promotes nasopharyngeal carcinoma through activation of Wnt/beta-catenin pathway. Eur Rev Med Pharmacol Sci 2018;22:3423-9.
12. Zhao L, Fong A, Liu N, Cho W. Molecular subtyping of nasopharyngeal carcinoma (NPC) and a microRNA-based prognostic model for distant metastasis. J Biomed Sci 2018;25:16.
13. Ribassin-Majed L, Marguet S, Lee A et al. What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis. J Clin Oncol 2017;35:498-505.
14. Hsu HC, Tsai SY, Wu SL et al. Longitudinal perceptions

of the side effects of chemotherapy in patients with gynecological cancer. Support Care Cancer 2017;25:3457-64.

15. Roth AD, Maibach R, Martinelli G et al. Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). Ann Oncol 2000;11:301-6.
16. Ge L, Li N, Yuan GW, Sun YC, Wu LY. Nedaplatin and paclitaxel compared with carboplatin and paclitaxel for patients with platinum-sensitive recurrent ovarian cancer. Am J Cancer Res 2018;8:1074-82.
17. Hong Q, Li O, Zheng W et al. LncRNA HOTAIR regulates HIF-1alpha/AXL signaling through inhibition of miR-217 in renal cell carcinoma. Cell Death Dis 2017;8:e2772.
18. Yang SW, Zhang ZG, Hao YX et al. HIF-1alpha induces the epithelial-mesenchymal transition in gastric cancer stem cells through the Snail pathway. Oncotarget 2017;8:9535-45.
19. Xiong J, Li J, Yang Q, Wang J, Su T, Zhou S. Gossypol has anti-cancer effects by dual-targeting MDM2 and VEGF in human breast cancer. Breast Cancer Res 2017;19:27.
20. Chen JY, Wu X, Hong CQ et al. Downregulated ECRG4 is correlated with lymph node metastasis and predicts poor outcome for nasopharyngeal carcinoma patients. Clin Transl Oncol 2017;19:84-90.