Intensity-modulated radiotherapy combined with endostar has similar efficacy but weaker acute adverse reactions than IMRT combined with chemotherapy in the treatment of locally advanced nasopharyngeal carcinoma

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Abstract

The present study is to compare the efficacy and adverse effects of intensity-modulated radiotherapy (IMRT) combined with endostar and IMRT combined with concurrent chemotherapy on locally advanced nasopharyngeal carcinoma (NPC).

A total of 23 patients with stage III-IVa NPC were included in the present study, and randomly divided into experimental group (10 cases treated with IMRT + endostar) and control group (13 cases treated with IMRT + chemotherapy of cis-dichlorodiamineplatinum). Endostar was intravenously administered from the first day of IMRT. The patients received a total of 2 cycles (14 days each) separating by a 7-day interval.

IMRT combined with endostar did not have significantly different recent efficacy compared with IMRT combined with chemotherapy. IMRT combined with endostar and IMRT combined with chemotherapy had 2-year overall survival (OS) rates of 100.0% and 69.6%, respectively, without significant difference between each other ($\chi^2 = 1.446, P = .299$). The 2-year local relapse-free survival (LRFS) of the 2 groups were 100.0% and 81.3%, respectively, without significant difference between each other ($\chi^2 = 1.000, P = .317$). The 2-year distant metastasis-free survival (DMFS) of the 2 groups were 100.0% and 73.5% ($\chi^2 = 1.591, P = .207$), respectively. The 2-year progression-free survival (PFS) of the 2 groups were 100.0% and 67.3% ($\chi^2 = 2.164, P = .141$), respectively. However, the cumulative survival curves of OS, LRFS, DMFS, and PFS were separated between the 2 groups. The result that IMRT combined with endostar did not have significantly different long-term efficacy than IMRT combined with chemotherapy probably due to limited case number and short follow-up time. IMRT combined with endostar resulted in significantly lower grades of leucopenia, nausea/vomiting, weight loss, and oral mucositis compared with IMRT combined with chemotherapy. The grades of late adverse reactions of IMRT combined with endostar were not different from those of IMRT combined with chemotherapy.

The present study demonstrates that, compared with IMRT combined with chemotherapy, IMRT combined with endostar has similar efficacy in the treatment of locally advanced NPC, but significantly weaker acute adverse reactions, which improve the life quality of NPC patients.

Abbreviations: CR = complete response, CT = computed Tomography, CTV1 = clinical target volume-1, CTV2 = clinical target volume-2, DFS = disease-free survival, DMFS = distant metastasis-free survival, EORTC = European Organization for Research and Treatment of Cancer, GTVnd = gross tumor volume of the positive cervical lymph node, GTVnx = gross tumor volume of the nasopharynx, IMRT = intensity-modulated radiotherapy, KPS = Karnofsky Performance Status, LRFS = local relapse-free survival, NCI-CTC = National Cancer Institute-Common Toxicity Criteria, NPC = nasopharyngeal carcinoma, NRFS = nodal relapse-free survival, OS = overall survival, PD = progressive disease, PDGFR = platelet-derived growth factor receptor, PFS = progression-free survival.
1. Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in South China, with its incidence in Guangxi province ranking the second in the world.\(^{1,15}\) Radiotherapy is the primary treatment method for NPC. As the improvement of technology, especially the development of intensity-modulated radiotherapy (IMRT), tumor local control rate has been dramatically enhanced, and overall 5-year survival has been significantly increased.\(^{12-14}\) Studies show that concurrent chemotherapy fails to improve the treatment effect of IMRT on locally advanced NPC.\(^{12-14}\) In addition, concurrent chemotherapy significantly increases III/IV hematological toxicity level and mucosal toxicity, and severely affects the treatment process and life quality of patients.\(^{15}\) Therefore, drugs with high efficiency and low toxicity that can replace concurrent chemotherapy for locally advanced NPC are drawing more and more attentions from researchers.

Endostar, independently developed by Chinese scholars, is a recombinant human endostatin constructed through adding 9 amino acid residues to the N-terminus of endostatin.\(^{16}\) Endostar has better stability against protease, acid and heat than endostatin.\(^{17}\) It inhibits the growth of a variety of tumors by blocking tumor angiogenesis, normalizes the structure and function of vasoganglion, improves blood circulation and tissue hypoxia, and enhances the radiosensitivity of hypoxic cells.\(^{18}\) Vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor-2 (VEGFR-2), and platelet-derived growth factor receptor (PDGFR) are the primary targets of the endostar. In clinical practice, endostar has efficacy in the treatment of non-small cell lung cancer, colorectal cancer, bone soft tissue sarcoma, metastatic malignant melanoma, gastric cancer, esophageal cancer, and cervical cancer.\(^{11,12,19-23}\)

However, there are few reports on the treatment of NPC using radiotherapy combined with antiangiogenic agents. The present study compares the efficacy and toxic side effects of IMRT combined with endostar and IMRT combined with concurrent chemotherapy on locally advanced NPC.

2. Materials and methods

2.1. Patients

A total of 23 patients with stage III-IVa NPC admitted at the First Affiliated Hospital of Guangxi Medical University between January and November 2013 were included in the present study. The patients were randomly divided into experimental group (10 cases treated with IMRT + endostar) and control group (13 cases treated with IMRT + chemotherapy). The experimental group included 8 males and 2 females, while the other 10 patients in experimental group, 4 cases had stage III NPC, and 6 cases had stage IV NPC. In addition, 2 cases out of the 10 patients had differentiated nonkeratinizing carcinoma, while the other 8 had undifferentiated non-keratinizing carcinoma. The control group included 11 males and 2 females, who were aged between 41 and 64 years with a median of 50.5 years. Clinically, 4 out of the 13 patients in control group had stage III NPC and 9 had stage IV NPC. Moreover, 3 cases out of the 13 patients had differentiated nonkeratinizing carcinoma, while the other 10 had undifferentiated non-keratinizing carcinoma. All patients were diagnosed with NPC by histopathological examinations. The general data of the 2 groups were comparable (Table 1). All procedures were approved by the Ethics Committee of Guangxi Medical University. Written informed consents were obtained from all patients or their families.

The inclusion criteria were: histopathological diagnosis of NPC; no distant metastasis by auxiliary examination; first diagnosis of NPC, without previous radiotherapy or chemotherapy; stage III-IVa according to the 7th Union for International Cancer Control staging standards; existence of NPC foci that were measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) standards; serum creatinine ≤ 1.25 times of UNL, or creatinine clearance rate ≥ 60 ml/minute; serum bilirubin ≤ 1.5 times of UNL; AST (SGOT) and ALT (SGPT) ≤ 2.5 times of UNL; and alkaline phosphatase ≤ 5 times of UNL; serum hemoglobin ≥ 10gm/dL, platelet count ≥ 100,000/µL, absolute neutrophil count ≥ 1,500/µL; Karnośky scores > 70; x) estimated overall survival > 6 months. The exclusion criteria were: symptomatic cerebral metastasis, bone marrow metastasis, cognitive disorders, or any distant metastasis; pregnancy or lactation; history of malignant tumors or other diseases; history of radiotherapy, chemotherapy or immunotherapy; severe bone marrow dysfunction; hemorrhagic tendency; drug abuse or alcohol addiction.

During the research period, patients who failed to follow medication plan or complete more than 80% of the plan were also excluded from the study. Patients who did not complete the study due to side effects were not used for curative effect analysis.

### Table 1

Clinical characteristics of patients.

| Clinical data | Radiotherapy + endostar (n = 10) | Radiotherapy + chemotherapy (n = 13) | P  |
|---------------|----------------------------------|------------------------------------|----|
| Age (years)   | Median 59 | 49 | .830 |
|              | Range 40–77 | 41–64 |    |
| Gender (No. of cases) | Male 8 | 11 | .772 |
|              | Female 2 | 2 |    |
| Pathological types | WHO I 0 | 0 | .859 |
|              | WHO II 2 | 3 |    |
|              | WHO III 8 | 10 |    |
| T staging (No. of cases) | T1 0 | 0 | .129 |
|              | T2 0 | 2 |    |
|              | T3 7 | 4 |    |
|              | T4 3 | 7 |    |
| N staging (No. of cases) | N0 2 | 1 | .204 |
|              | N1 2 | 0 |    |
|              | N2 4 | 10 |    |
|              | N3 2 | 2 |    |
| Clinical staging (No. of cases) | III 4 | 4 | .645 |
|              | IV 6 | 9 |    |
2.5. Adverse reaction evaluation

To evaluate acute adverse reactions every week, National Cancer Institute-Common Toxicity Criteria (NCI-CTC) was employed. To evaluate recent efficacy, physical examination, nasopharyngeal fiberoscopy, and MRI were performed 3 months after treatments. The data showed that IMRT combined with endostar resulted in a CR rate of 60% (6/10) and a PR rate of 40% (4/10). In addition, IMRT combined with chemotherapy led to a CR rate of 61.5% (8/13) and a PR rate of 38.5% (5/13). There was no statistically significant difference between the 2 groups ($\chi^2=0.006, P=.94$) (Table 2). The result suggests that IMRT combined with endostar does not have significantly different recent efficacy compared with IMRT combined with chemotherapy.

2.6. Follow-ups

Tumor regression and acute adverse reactions were recorded every week during treatment. Three months after radiotherapy, the recent efficacy was evaluated. Within 2 years after treatment, the patients were examined every 3 months. From the 3rd to the 5th years after treatment, the patients were examined every 6 months. After 5 years, the patients were examined annually. During each follow-up, the patients received physical examination, chest radiography, abdominal ultrasound, nasopharyngeal fiberoscopy, and laboratory examinations. Late radiation injury was examined using RTOG/EORTC staging standards. Head and neck MRI was performed every 6 months. Biopsy was performed on patients suspected with recurrence. Chest and abdominal CT and bone isotope scan were carried out on patients suspected with distant metastasis. The follow-ups were terminated on April 1, 2016, with a median duration of 36 months, ranging from 27 to 38 months. The parameters for analysis included overall survival (OS), disease-free survival (DFS), local relapse-free survival (LRFS), nodal relapse-free survival (NRFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS). Survival time calculation started on the first day of diagnosis.

2.7. Statistical analysis

All results were analyzed using SPSS 18.0 software (IBM, Armonk, NY). Kaplan–Meier method was used to calculate survival rates. Log-rank test was employed to examine the significance of survival rate differences. COX proportional hazard model was used for univariate and multivariate analyses, as well as the calculation of relative hazard ratio. Multivariate analysis was performed using the backward method. Hematological toxicity and nonhematologic toxicity of the 2 groups were compared using the $\chi^2$ test. Differences with $P<.05$ were considered statistically significant.

3. Results

3.1. IMRT combined with endostar does not have significantly different recent efficacy compared with IMRT combined with chemotherapy

To evaluate recent efficacy, physical examination, nasopharyngeal fiberoscopy, and MRI were performed 3 months after treatments. The data showed that IMRT combined with endostar resulted in a CR rate of 60% (6/10) and a PR rate of 40% (4/10). In addition, IMRT combined with chemotherapy led to a CR rate of 61.5% (8/13) and a PR rate of 38.5% (5/13). There was no statistically significant difference between the 2 groups ($\chi^2=0.006, P=.94$) (Table 2). The result suggests that IMRT combined with endostar does not have significantly different recent efficacy compared with IMRT combined with chemotherapy.

3.2. IMRT combined with endostar does not have significantly different long-term efficacy than IMRT combined with chemotherapy

To evaluate long-term efficacy, the patients were followed-up for 27 to 38 months with a median of 36 months. For all patients, the 2-year OS rate was 78.9%, with 2 case of local recurrence, 3 cases of distant metastasis and 1 case being dead. The 2-year LRFS, DMFS, and PFS for all patients were 87.3%, 82.1%, and 77.7%, respectively. IMRT combined with endostar and IMRT combined with chemotherapy had 2-year OS rates of 100.0% and
69.6%, respectively, without significant difference between each other \((\chi^2 = 1.446, P = .299)\). The 2-year LRFS of the 2 groups were 100.0% and 81.3%, respectively, without significant difference between each other \((\chi^2 = 1.000, P = .317)\). The 2-year DMFS of the 2 groups were 100.0% and 73.5% \((\chi^2 = 1.591, P = .207)\), respectively. The 2-year PFS of the 2 groups were 100.0% and 67.3% \((\chi^2 = 2.164, P = .141)\), respectively. However, the cumulative survival curves of OS, LRFS, DMFS, and PFS were separated between the 2 groups (Fig. 1). The results indicate that IMRT combined with endostar does not have significantly different long-term efficacy than radiotherapy combined with chemotherapy.

### 3.3. IMRT combined with endostar results in significantly lower grades of leucopenia, nausea/vomiting, weight loss, and oral mucositis compared with IMRT combined with chemotherapy

To evaluate acute adverse reactions, NCI-CTC was used. The common acute adverse reactions included leucopenia, neutropenia, hemoglobin decrease, nausea/vomiting, weight loss, and acute oral mucositis. No dysfunction of liver, kidney, or heart was observed in either group. In the group of IMRT combined with endostar, the occurrence rates of leucopenia with grades 0, 1 and 2 were 50.0%, 20.0%, and 30.0%, respectively. In the group of IMRT combined with chemotherapy, the occurrence rates of leucopenia with grades 0, 1, 2, and 3 were 7.7%, 23.1%, 53.8%, and 15.4%, respectively. The 2 groups had significant difference in leucopenia rate \((Z = 8.215, P = .042)\). In the group of radiotherapy combined with endostar, the occurrence rates of nausea/vomiting with grades 0, 1, and 2 were 40.0%, 50.0%, and 10.0%, respectively. In the group of IMRT combined with chemotherapy, the occurrence rates of nausea/vomiting with grades 2 and 3 were 84.6% and 15.4%, respectively. The 2 groups had significant difference in nausea/vomiting rates.
(Z = 19.270, P < .001). In the group of IMRT combined with endostar, the occurrence rates of weight loss with grades 0, 1 and 2 were 80.0%, 10.0%, and 10.0%, respectively. In the group of IMRT combined with chemotherapy, the occurrence rates of weight loss with grades 1 and 2 were 61.5%, and 38.5%, respectively. The 2 groups had significant difference in weight loss rate (Z = 15.992, P < .001). In the group of IMRT combined with endostar, the occurrence rates of oral mucositis with grades 0, 1 and 2 were 30.0%, 50.0% and 20.0%, respectively. In the group of IMRT combined with chemotherapy, the occurrence rates of oral mucositis with grades 1, 2 and 3 were 15.4%, 61.5% and 23.1%, respectively. The 2 groups had significant difference in oral mucositis rate (Z = 10.676, P = .014). In addition, no significant differences were observed in hemoglobin decrease, thrombocytopenia, dry mouth or skin reactions between the 2 groups (P > .05) (Table 3). These results suggest that IMRT combined with endostar results in significantly lower grades of leucopenia, nausea / vomiting, weight loss and oral mucositis compared with IMRT combined with chemotherapy.

3.4. The grades of late adverse reactions of IMRT combined with endostar are not different from those of IMRT combined with chemotherapy

To evaluate late adverse reactions, the parameters such as dry mouth, subcutaneous soft tissue fibrosis, hearing loss, limitation of mouth opening, cranial nerve paralysis, temporal lobe necrosis, and decreased vision were studied 2 years after IMRT. For both groups, no adverse reactions with grades 3 or 4 were observed. There was no significant difference between the 2 groups (P > .05) (Table 4). The result indicates that the grades of late adverse reactions of IMRT combined with endostar are not different from those of IMRT combined with chemotherapy.

4. Discussion

It has been reported that tumor growth is related with angiogenesis in 1971.[23,24] O’Reilly et al.[25] demonstrate that endostatin inhibits the growth of tumors by inhibiting the proliferation of vascular endothelial cells. Later, Wang et al.[26] have shown good efficacy of endostar combined with vinorelbine and cisplatin in the treatment of advanced non-small cell lung cancer. Around 22 patients were analyzed with stage rIII-IVb and cisplatin in the treatment of advanced non-small cell lung cancer. Around 22 patients were analyzed with stage rIII-IVb and cisplatin in the treatment of advanced non-small cell lung cancer. Around 22 patients were analyzed with stage rIII-IVb and cisplatin in the treatment of advanced non-small cell lung cancer.

The results of the present study show that IMRT combined with endostar does not have significantly different recent efficacy compared with IMRT combined with chemotherapy. Although 2-year OS, LRFs, DMFs, and PFS are not significantly different between the 2 groups, but the cumulative survival curves were separated between the 2 groups, indicating that IMRT combined with endostar has better long-term efficacy compared with radiotherapy combined with chemotherapy. This might be due to the limited sample size and short follow-up duration. The mechanisms by which endostar enhances treatment efficacy may be the following: endostar blocks vascular endothelial growth factor that stimulates vascular endothelial cell proliferation, inhibits its apoptosis, promotes blood vessel construction, and facilitates lymphangiogenesis and lymphatic metastasis; endostar improves disordered vascular network, blood circulation, and hypoxia, and enhances the radiation sensitivity of hypoxic cells; endostar facilitates cell cycle redistribution, promoting the effects of endostar and radiotherapy in different cell cycle phases.

The acute adverse reactions during the treatment include leucopenia, neutropenia, hemoglobin decrease, nausea/vomiting, weight loss, and oral mucositis. The most significant acute adverse reaction is nausea/vomiting. For the group treated with IMRT combined with chemotherapy, 5-hydroxytryptamine-3 receptor antagonist was used to stop nausea/vomiting. By contrast, the group treated with IMRT combined with endostar received no antiemetic drugs, but still had reduced degree of nausea/vomiting compared with the other group, suggesting that IMRT combined with endostar had milder acute toxic side effects. In addition, the group treated with IMRT combined with chemotherapy had more severe oral mucositis, and led to eating difficulties that, together with severe nausea/vomiting, caused more severe weight loss. The grade of leucopenia in the group treated with IMRT combined with endostar is significantly different from that in the other group, indicating that IMRT combined with chemotherapy is more likely to cause myelosuppression. After treatment with recombinant human granulocyte colony stimulating factor, the white blood cells in patients with

### Table 3

| Acute adverse reactions in the 2 groups [No. of cases (%)]. | Radiotherapy combined with endostar | Radiotherapy combined with chemotherapy |
|------------------------------------------------------------|------------------------------------|----------------------------------------|
|                                                           | 0 1 2 3 4                          | 0 1 2 3 4                                |
| Leucopenia                                                 | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (23.1) 3 (32.1)          |
| Hemoglobin decrease                                        | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (23.1) 3 (32.1)          |
| Thrombocytopenia                                           | 0 (0) 10 (76.9)                    | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |
| Nausea/vomiting                                            | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |
| Weight loss                                                | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |
| Oral mucositis                                             | 0 (0) 10 (76.9)                    | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |
| Skin reaction                                              | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |
| Dry mouth                                                  | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |
| Liver dysfunction                                          | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |
| Renal dysfunction                                          | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |
| Cardiac dysfunction                                        | 0 (0) 1 (7.7) 2 (20.0) 3 (30.0)     | 0 (0) 1 (7.7) 2 (15.4) 10 (76.9)         |

Report that endostar combined with IMRT significantly inhibits the growth of NPC xenografts in nude mice, probably because endostar reduces vascular endothelial growth factor expression that is necessary for the repair of damaged tumor vascular endothelial cells. Other studies demonstrate that endostar reduces metastatic ability of HNE-1 cells and inhibits vasculo- genic mimicry formation in vitro,[28] and that endostar inhibits the formation of tumor vascular endothelial cells of CNE-2 xenograft tumor and tumor growth in nude mice.[29–31]
myelosuppression returned to normal. In addition, none of the patients in the study had liver, heart, or kidney dysfunction. The group treated with IMRT combined with chemotherapy used liver protective drugs, which might have alleviated the liver toxicity effect of chemotherapy drugs. In summary, antiangiogenic therapy has been playing important roles in the treatment of malignant tumors. Compared with IMRT combined with chemotherapy, IMRT combined with endostar has similar efficacy but lower acute toxic reactions, which may be helpful in improving the life quality of patients with locally advanced NPC.

Author contributions

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