

Original Article

Sensitization of nedaplatin added to three-dimensional conformal radiotherapy in advanced esophageal cancer

Feng Ding¹, Kai Li¹, Zhongzhong Peng², Yanli Zhang³, Lishenquan Cai⁴

¹The Second Department of Radiotherapy, ²The First Department of Radiotherapy, Departments of ³Medical Oncology, ⁴Radiotherapy Technology, Ningbo No.2 Hospital, Ningbo, Zhejiang Province, China

Received November 26, 2017; Accepted December 31, 2017; Epub February 15, 2018; Published February 28, 2018

Abstract: Objective: To compare the short-and long-term efficacy and safety of three-dimensional conformal radiotherapy in combination with nedaplatin versus three-dimensional conformal radiotherapy alone in treating patients with advanced esophageal cancer. Methods: Ninety-four patients with confirmed intermediate or advanced esophageal cancer treated in our hospital from June 2012 to August 2013 were recruited in this study. All the patients were randomly assigned to the control group (n=47) or the observation group (n=47) by a random number table. All the patients in both groups were treated with three-dimensional conformal radiotherapy. The patients in the observation group also received additional nedaplatin injection on day 1 of weekly three-dimensional conformal radiotherapy. The short-term efficacy, acute toxicity of chemoradiotherapy, carcinoembryonic antigen (CEA) values and survival of the patients were compared between in the two groups. Results: The response rate was 53.19% (25/47) in the control group versus 80.85% (38/47) in the observation group, with significant difference ($\chi^2=5.034$, $P<0.05$). At 2 months after treatment, the CEA value in the observation group (6.63 ± 3.11 ng/ml) was markedly lower than that in the control group (8.02 ± 5.13 ng/ml; $P<0.05$). The incidences of granulocytopenia and thrombocytopenia in the observation group were 53.19% (25/47) and 40.43% (19/47) respectively, which were strikingly higher than those (25.53% (12/47) and 23.40% (11/47), respectively) in the control group ($P<0.05$). Mild differences between the two groups were noted in the incidences of acute radiotherapy toxicity and adverse gastrointestinal reactions ($P>0.05$). The 1-year, 2-year, 3-year overall survival rates in the observation group were 72.34% (34/47), 51.06% (24/47) and 34.04% (16/47), respectively; the corresponding rates in the control group were 53.19% (25/47), 31.91% (15/47) and 19.15% (9/47), respectively, with the overall survival rates in favor of the observation group ($P<0.05$). Conclusion: Nedaplatin, a second-generation platinum compound featuring confirmed good response and tolerance, and radiotherapy sensitization similar to cisplatin, is of great significance to improve the quality of life of patients with advanced esophageal cancer, prolong the survival of patients and offers more alterations for the future treatment.

Keywords: Chemotherapy sensitization, nedaplatin, three-dimensional conformal radiotherapy, intermediate and advanced, esophageal cancer

Introduction

Esophageal cancer is a clinically common malignant tumor, and the disease occurred in 22.14 per 10,000 patients in 2016 according to the epidemiological statistics [1]. China is one of the countries with the highest incidence of esophageal cancer. Nearly 50% of the patients with esophageal cancer worldwide were in China owing to its large population. More than 70% of the patients had been found to be in intermediate or advanced stages of esophageal cancer when they were initially confirmed. Prognosis of the patients is poor even after surgical resection [2]. Radiotherapy is the

treatment of choice for intermediate or advanced patients who miss the chance of surgical treatment as they have certain response to radiotherapy. Nevertheless, statistically, three-dimensional conformal radiotherapy alone is associated with less than 30% of 5-year survival in the patients [3]. The use of sensitization or chemotherapy and other adjuvant treatment to lower recurrence of local esophageal cancer and improve the 5-year survival remains the primary strategy for intermediate or advanced esophageal cancer. Nedaplatin, also known as cis-glycolic acid diammine platinum, is a new-generation platinum injection developed by Shionogi & Co, a Japanese pharmaceutical

Sensitization of nedaplatin plus three-dimensional conformal radiotherapy

company. Nedaplatin has proven to be analogous to cisplatin and has the effect of chemotherapy sensitization, but with less toxicity. However, there are few relevant reports in China [4]. Therefore, in this study, we recruited 94 patients with intermediate or advanced esophageal cancer treated in our hospital from June 2012 to August 2013, with the aim to compare the short-term and long-term efficacy and safety between three-dimensional conformal radiotherapy plus synchronous nedaplatin chemotherapy and three-dimensional conformal radiotherapy alone in treating esophageal cancer.

Materials and methods

Patients

From June 2012 to August 2013, 94 patients with intermediate or advanced esophageal cancer who were treated in our hospital were enrolled in this study. Patients were eligible for enrollment if they had pathologically confirmed squamous cell carcinoma with measurable lesions, an age ranging from 38 to 78 years, no distant metastasis as demonstrated by CT, MRI and other radiographic approaches, assessed potential survival of more than 6 months, stable vital signs, were so well-communicated that they could understand the physician's orders, Karnofsky performance status (KPS) score ≥ 70 , the patients and their families were informed of the study and voluntary to participate in this study and provided written informed consent. Patients were excluded if they had severe dysfunctions in the heart, the liver, the kidney or other important organs, pre-perforation signs (including giant ulcer, bent deformity), with active esophageal variceal bleeding or concomitantly participated in another trial [5].

All the eligible patients were randomly assigned by a random number table to the control group ($n=47$) or the observation group ($n=47$). In the control group, 27 patients were males and 20 were females, with an age ranging from 38 to 76 years (mean, 65.87 ± 3.69 years); among the 47 patients, advanced esophageal cancer of Stage II was reported in 9 patients, Stage III in 24 patients and Stage IV in 14. In the observation group, there were 29 males and 18 females, aged 40-78 years (mean, 64.35 ± 3.14 years); among the 47 patients, advanced esophageal cancer of Stage II occurred in 11

patients, Stage III in 23 patients and Stage IV in 13. The protocol of this study was conducted after approval by the medical ethics committee of our hospital. The differences of the data at baseline were statistically insignificant between the two groups ($P > 0.05$).

Methods

All the patients in both groups underwent three-dimensional conformal radiotherapy. In addition to three-dimensional conformal radiotherapy, the patients in the observation group were also treated with Nedaplatin for Injection (Nanjing Xianshengdongyuan Pharmaceutical Co. Ltd, Chinese Drug Approval Number H20030884) on day 1 of weekly radiotherapy, at a recommended dose of 80-100 mg/m². Nedaplatin for Injection was dissolved in 0.9% NaCl solution, and then diluted to 500 ml which was intravenously infused at an appropriate speed for no less than 60 min. The treatment lasted for 6 weeks, with 6 times of infusions in total.

Outcome measures

CT or MRI or electronic gastroscope reviews of the chest was performed within 2 months after the end of the treatment, the short-term efficacy of the patients in both groups was evaluated according to the WHO scoring system and RECIST (Response Evaluation Criteria In Solid Tumor). Complete response (CR) was defined as disappearance of all target lesions for at least 4 weeks; partial response (PR) was defined as at least a 50% decrease in the sum of the longest diameter of target lesions for at least 4 weeks, with no appearance of new lesions; stable disease (SD) was defined as no more than a 50% decrease or no more than a 25% increase in the sum of the longest diameter of target lesions for at least 4 weeks, with no appearance of new lesions; progressive disease (PD) defined as at least a 25% increase in the sum of the longest diameter of target lesions or appearance of new lesions. Overall response rate = $(CR + PR) / \text{Total number of cases} \times 100\%$. During the treatment phase of the study, close observation to diet, sleep, and physical conditions of the patients, and weekly reviews of blood routine examination, renal and hepatic functions were conducted in the patients. Acute toxicity of radiotherapy and chemotherapy were also recorded, with the toxicity to chemothera-

Sensitization of nedaplatin plus three-dimensional conformal radiotherapy

Table 1. Comparison of the response to the treatment between the two groups (n, %)

Variable	Case	CR	PR	SD	PD	Overall response rate
Observation group	47	25	13	6	3	38 (80.85)
Control group	47	17	8	13	5	25 (53.19)
χ^2	-	-	-	-	-	6.774
P	-	-	-	-	-	<0.05

Note: CR, complete response; PR, partial response; SD, stable disease, with no appearance of new lesions; PD, progressive disease.

Table 2. Comparison of CEA values between two groups before and after treatment (ng/ml)

Variable	Case	Preoperative CEA	Postoperative CEA
Observation group	47	9.14±5.25	6.63±3.11
Control group	47	9.23±4.78	8.02±5.13
t	-	0.004	6.118
P	-	>0.05	<0.05

Note: CEA, carcinoembryonic antigen.

py graded by the WHO toxicity grading standards and toxicity to radiotherapy graded by the Radiation Therapy Oncology Group (RTOG) radiation toxicity scale. The long-term efficacy of 3-year survival was assessed among the patients who were followed up to August 2016. Additionally, the carcinoembryonic antigen (CEA) values were examined before treatment and at 2 months after treatment [6].

Statistical analysis

All the clinical data pooled in this study were input into the Excel database and then analyzed by two independent teams of professional medical statisticians with the use of the SPSS statistical software, version 21.0. Measurement data with normal distribution were analyzed using the t-test, whereas count data were evaluated with the application of the chi-square test. The P value of less than 0.05 was set as the results to be statistically significant. In the later phase of the study, the data and statistics results were checked by the person responsible to the study.

Results

Short-term efficacy

The response rates differed markedly between the control group and the observation group

(53.19% (25/47) versus 80.85% (38/47); $\chi^2=5.034$, $P<0.05$), implying that nedaplatin added to three-dimensional conformal radiotherapy significantly improved the short-term efficacy of patients (**Table 1**).

Tumor markers

CEA values were slightly different between the two groups before treatment ($P>0.05$); but the CEA value of the observation group was substantially lower than that of the control group at 2 months after treatment ($P<0.05$, **Table 2**).

Toxicity

No discontinuation of the study drugs due to intolerance to severe adverse gastrointestinal reactions occurred in the patients, and the adverse response was resolved after symptomatic treatment. Granulocytopenia was reported in 53.19% (25/47), and thrombocytopenia in 40.43% (19/47) of the patients in the observation group, which were strikingly higher than those (25.53% (12/47), 23.40% (11/47)) of the patients in the control group ($P<0.05$). The incidences of acute toxicity of radiotherapy and adverse gastrointestinal reactions differed insignificantly between the two groups ($P>0.05$). All this suggests higher safety of three-dimensional conformal radiotherapy combined with nedaplatin (**Table 3**).

Follow up

The 1-year, 2-year, and 3-year overall survival rates in the observation group were 72.34%, 51.06% and 34.04%, respectively. The corresponding rates in the control group were 53.19%, 31.91% and 19.15%, respectively. All the above overall survival rates were remarkably higher in the observation group than in the control group (All $P<0.05$, **Table 4**).

Discussion

Radiotherapy is an important technique in comprehensive cancer treatment. Theoretically, the tumor cells can be killed as long as the radiation dose is adequately high. However, it is undesirable in clinical practice, primarily for which is the radiation dose at the lesion site is

Sensitization of nedaplatin plus three-dimensional conformal radiotherapy

Table 3. Comparison of toxicity between two groups (n, %)

Item	Observation group (n=47)					Control group (n=47)				
	Grade 0	Grade I	Grade II	Grade III	Grade IV	Grade 0	Grade I	Grade II	Grade III	Grade IV
	Granulocytopenia	22	16	7	2	0	35	12	0	0
Thrombocytopenia	28	10	7	2	0	36	6	5	0	0
Gastrointestinal reaction	27	9	10	1	0	28	10	6	3	0
Radiation esophagitis	25	10	8	4	0	24	8	10	5	0
Radiation pneumonitis	36	7	4	0	0	37	5	5	0	0
Radiation dermatitis	32	8	5	2	0	33	7	5	2	0

Table 4. Comparison of the 1-year, 2-year, and 3-year overall survival between the two groups (n, %)

Variable	Case	1-year overall survival rate	2-year overall survival rate	3-year overall survival rate
Observation group	47	34 (72.34)	24 (51.06)	16 (34.04)
Control group	47	25 (53.19)	15 (31.91)	9 (19.15)
χ^2	-	7.114	6.328	4.002
P	-	<0.05	<0.05	<0.05

restricted by the tolerance of the lung, the heart and the spinal cord surrounding the tumor lesions to radiation. Three-dimensional conformal radiotherapy is one of the key breakthroughs in the radiotherapy techniques. Advanced from the plane irradiation to the three-dimensional irradiation, locally higher dose in the lesions and lower dose in the adjacent normal tissues are achieved [7]. Despite the increasing advance in radiotherapy and the growing update of the accelerator, the 5-year survival rate has not been improved with radiotherapy alone. The failure is still mainly attributable to low sensitivity to radiation, local recurrence or distant metastasis of the tumor cells [8]. Concurrent chemotherapy and radiotherapy are targeted both locally and systematically, and some chemotherapy agents also have certain sensitizing effect on chemotherapy. Over recent years, it has become the focus of the research on treating intermediate or advanced esophageal cancer in patients who is intolerable to surgery.

Some chemotherapy drugs including camptothecins, platinum and taxanes have proven to have certain radiosensitization effect [9]. Among them, antineoplastic drugs platinum are one of the major categories. Statistically, more than seventy percent of the chemotherapy regimens for cancer contain platinum com-

pounds [10]. Years of clinical observation has substantiated that cisplatin is associated with severe adverse gastrointestinal reactions and nephrotoxicity. As a result, the patients find it difficult to follow the physician's order. Accordingly, anti-cancer experts have been striving to develop safer alternatives [11]. Nedaplatin

is a second generation platinum compound. An analysis on clinical data has revealed that nedaplatin has a relatively broad anti-tumor spectrum, to some extent, taking small cell lung cancer, non-small cell lung cancer, esophageal cancer, head and neck cancer and other solid tumors under control [12]. Moreover, the water solubility of nedaplatin is 900% higher than that of cisplatin. No need of hydration, it is more convenient for medication. Nedaplatin use also results in shorter hospital stay, which is helpful to improve the turnover rate of the inpatient beds in the hospital [13]. In addition, studies have shown that nedaplatin and cisplatin are not completely cross resistant, so some patients tolerant to cisplatin may use nedaplatin instead. In our current study, the results showed significant differences in the response rate between the two groups, 80.85% (38/47) in the observation group versus 53.19% (25/47) in the control group ($\chi^2=5.034$, $P<0.05$). At 2 months after treatment, the CEA value of the observation group lowered more considerably than that of the control group ($P<0.05$). The 1-year, 2-year, 3-year overall survival rates of the observation group were strikingly higher than those of the control group ($P<0.05$). These results indicate that nedaplatin added to three-dimensional conformal radiotherapy has a synergistic effect and improves the sensitivity of radiotherapy. Jang and colleagues argued that

Sensitization of nedaplatin plus three-dimensional conformal radiotherapy

nedaplatin had a definite sensitizing effect after they had investigated the sensitizing effect of nedaplatin on radiotherapy in oral cancer, lung cancer, esophageal cancer and other malignant tumors and found more than 80% of response rates in all the patients [14, 15].

Toxicity of nedaplatin is different from that of cisplatin. The dose-limiting toxicity of nedaplatin is myelosuppression-induced thrombocytopenia, the incidence of which is approximately 40%. The adverse gastrointestinal reactions and renal toxicity with nedaplatin are fewer than those with cisplatin. The incidence of myelosuppression with nedaplatin is higher, although slightly. There are clinically better symptomatic protocols. The patients complained of less pain and higher compliance. Our current study revealed that the rate of granulocytopenia in the observation group (53.19% (25/47)) was remarkably higher than 25.53% (12/47) in the control group ($P < 0.05$). The rate of thrombocytopenia was 40.43% (19/47) in the observation group, substantially higher than 23.40% (11/47) in the control group ($P < 0.05$). Nevertheless, the rates of acute radiation toxicity, reverse gastrointestinal reactions were insignificantly different between the two groups ($P > 0.05$). The result of the current study demonstrated a higher response rate, and lower gastrointestinal response and nephrotoxicity. Most elderly patients are intolerable to surgical treatment due to the intermediate or advanced stage and various underlying diseases [16, 17]. Nevertheless, the 5-year survival rate is merely approximately 20% with radiotherapy alone, so the disease is difficult to treat [18]. Moreover, the special anatomical structure of esophageal carcinoma in the neck and upper thoracic regions adds to the difficulty of resection, and there are more postoperative complications and a higher mortality. Thus, concurrent chemoradiotherapy is still the most important therapeutic strategies [19]. By contrast, the 5-fluorouracil-based concurrent chemoradiotherapy is associated with high incidences of radiation esophagitis and adverse gastrointestinal reactions, which in turn results in many patients' discontinuation of the therapy owing to resistance [20]. As compared with previous therapies, three-dimensional conformal radiotherapy in combination with nedaplatin leads

to more satisfactory short- and long-term efficacy, and lower toxicity, and provides a safer and more effective therapeutic strategy for elderly patients with esophageal cancer whose lesions are located in the neck and upper thoracic regions.

In conclusion, nedaplatin, a second-generation platinum compound with confirmed good response and tolerance, has a radiosensitization effect similar to cisplatin. It is of great value in improving the tolerance and prolonging survival of patients with advanced esophageal cancer. Additionally, it also provides more alternatives for future treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Feng Ding, The Second Department of Radiotherapy, Ningbo No.2 Hospital, No.41 Northwest Street, Haishu District, Ningbo 315010, Zhejiang Province, China. Tel: +86-0574-83870232; E-mail: dingfeng1642@163.com

References

- [1] Yang JR, Jin HK and Jiang XY. The analysis of clinical effects of concurrent IMRT and nedaplatin on local- regional advanced esophageal carcinoma. *Journal of Clinical Medicine in Practice* 2011; 15: 75-77.
- [2] Edeline J, Boucher E, Rolland Y, Vauleon E, Pracht M, Perrin C, Le Roux C and Raoul JL. Comparison of tumor response by response evaluation criteria in solid tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. *Cancer* 2012; 118: 147-156.
- [3] Zhou JY, You SY and Peng KM. Three-dimensional conformal radiotherapy in combination with platinum and paclitaxel in the treatment of esophageal cancer. *The Practical Journal of Cancer* 2012; 27: 486-488.
- [4] Li AD and Peng KG. Preoperative concurrent chemoradiotherapy for esophageal cancer. *Chinese Journal of General Practice* 2014; 12: 1466-1468.
- [5] Bi LW, Zhang LZ and Zhou HF. Docetaxel and nedaplatin combined with concurrent conformal intensity-modulated radiotherapy in esophageal cancer. *Chinese Journal of Oncology* 2012; 34: 710-711.
- [6] Li YY, Lin HQ, Zhang LL, Feng LL, Niu SQ, Wang HY, Zhang YJ and Wang XC. Intensity-modulated radiotherapy has superior outcomes to three-dimensional conformal radiotherapy in

Sensitization of nedaplatin plus three-dimensional conformal radiotherapy

- patients with stage IE-IIIE extranodal nasal-type natural killer/T-cell lymphoma. *Oncotarget* 2017; 8: 60504-60513.
- [7] Ming BC, Luo ZG, Hu J, Luo M and Zhang SF. Clinical analysis of radiotherapy plus paclitaxel and nedaplatin in esophageal carcinoma. *Journal of Modern Oncology* 2013; 21: 559-562.
- [8] Lin XD, Shi XY, Zhou TC and Zhang WJ. Intensity-modulated radiation therapy versus three-dimensional conformal radiotherapy plus TP chemotherapy in locally advanced esophageal carcinoma. *Journal of Southern Medical University* 2011; 31: 1264-1267.
- [9] Cai JD, Liu J, Zeng SC, Cui YL, Li JH and Wang RF. Three-dimensional conformal radiotherapy combined with weekly dose nedaplatin and high-frequency hyperthermia in advanced esophageal cancer. *Journal of Modern Oncology* 2013; 21: 2715-2718.
- [10] Zhou SY. Efficacy of nedaplatin added to conformal radiotherapy in advanced esophageal cancer. *Chinese Journal of Clinical Oncology and Rehabilitation* 2012; 334-335.
- [11] Bae BK, Kang MK, Kim JC, Kim MY, Choi GS, Kim JG, Kang BW, Kim HJ and Park SY. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol J* 2017; 35: 208-216.
- [12] Pan R, Wang J, Qi F and Liu R. Dosimetric comparison and observation of three-dimensional conformal radiotherapy for recurrent nasopharyngeal carcinoma. *Oncol Lett* 2017; 14: 4741-4745.
- [13] Zhang TY, Huang WB, Bai YJ, Yang WB, Li N, Yue GJ and Xing SY. Three-dimensional conformal chemotherapy combined with nedaplatin and tegafur radiotherapy for 39 patients with advanced esophageal cancer. *Guizhou Medical Journal* 2013; 37: 214-216.
- [14] Jang HJ, Lee HS, Kim MS, Lee JM and Zo JI. Patterns of lymph node metastasis and survival for upper esophageal squamous cell carcinoma. *Ann Thorac Surg* 2011; 92: 1091-1097.
- [15] Van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW and van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; 366: 2074-2084.
- [16] Hirakawa H, Kiba T, Saito Y, Watanabe Y, Suzuki T and Ota N. Nedaplatin as a single-agent chemotherapy may support palliative therapy for patients with adenoid cystic carcinoma: a case report. *Case Rep Oncol* 2017; 10: 783-789.
- [17] Oshita F, Murakami S, Kondo T, Saito H, Yamada K and Nakayama Y. Nedaplatin and irinotecan with concurrent thoracic radiotherapy followed by docetaxel consolidation in patients with locally advanced non-small cell lung cancer. *J Exp Ther Oncol* 2017; 12: 17-23.
- [18] Yamashita H, Abe O and Nakagawa K. Involved-field irradiation concurrently combined with nedaplatin/5-fluorouracil for inoperable esophageal cancer on basis of 18FDG-PET scans: a long follow-up results of phase II study. *Radiother Oncol* 2017; 123: 488.
- [19] Kawarada Y, Miyazaki M, Itoh A, Araki R, Iwamizu H, Kataoka T, Kumakura Y, Ota A, Nagai T and Yamada K. Incidence of and risk factors associated with nedaplatin-related hypersensitivity reactions. *Int J Clin Oncol* 2017; 22: 593-599.
- [20] Asaka S, Shimakawa T, Yamaguchi K, Murayama M, Shimazaki A, Katsube T and Naritaka Y. The influence of neoadjuvant chemotherapy with docetaxel, nedaplatin and 5-fluorouracil after esophagectomy. *Anticancer Res* 2016; 36: 6165-6171.