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

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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 40.43% (19/47) respectively, while 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
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 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 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 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 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 for at least 4 weeks, with no appearance of new lesions; overall response rate=(CR+PR)/Total number of cases *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-
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**Table 1.** Comparison of the response to the treatment between the two groups (n, %)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Overall response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>47</td>
<td>25</td>
<td>13</td>
<td>6</td>
<td>3</td>
<td>38 (80.85%)</td>
</tr>
<tr>
<td>Control group</td>
<td>47</td>
<td>17</td>
<td>8</td>
<td>13</td>
<td>5</td>
<td>25 (53.19%)</td>
</tr>
<tr>
<td>χ²</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.774</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>Preoperative CEA</th>
<th>Postoperative CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>47</td>
<td>9.14±5.25</td>
<td>6.63±3.11</td>
</tr>
<tr>
<td>Control group</td>
<td>47</td>
<td>9.23±4.78</td>
<td>8.02±5.13</td>
</tr>
<tr>
<td>t</td>
<td>-</td>
<td>0.004</td>
<td>6.118</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Note: CEA, carcinoembryonic antigen.

The response rates differed markedly between the control group and the observation group (53.19% (25/47) versus 80.85% (38/47); χ²=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).

This all 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...
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restricted by the tolerance of the lung, the heart
and the spinal cord surrounding the tumor
lesions to radiation. Three-dimensional confor-
mal radiotherapy is one of the key break-
throughs 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 adja-
cent 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 radio-
therapy alone. The failure is still mainly attribut-
able to low sensitivity to radiation, local recur-
rence or distant metastasis of the tumor cells
[8]. Concurrent chemotherapy and radiothera-
py are targeted both locally and systematically,
and some chemotherapy agents also have cer-
tain 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 intolera-
table to surgery.

Some chemotherapy drugs including camptoth-
ceins, platinums and taxanes have proven to
have certain radiosensitization effect [9].
Among them, antineoplastic drugs platinums
are one of the major categories. Statistically,
more than seventy percent of the chemothera-
py 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 in-
patient beds in the hospital [13]. In addition,
studies have shown that nedaplatin and cispla-
atin are not completely cross resistant, so some
patients tolerant to cisplatin may use nedapla-
atin 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 consider-
ably than that of the control group ($P<0.05$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>1-year overall survival rate</th>
<th>2-year overall survival rate</th>
<th>3-year overall survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>47</td>
<td>34 (72.34)</td>
<td>24 (51.06)</td>
<td>16 (34.04)</td>
</tr>
<tr>
<td>Control group</td>
<td>47</td>
<td>25 (53.19)</td>
<td>13 (27.66)</td>
<td>9 (19.15)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>-</td>
<td>7.114</td>
<td>6.328</td>
<td>4.002</td>
</tr>
<tr>
<td>$P$</td>
<td>-</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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

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

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