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ORIGINAL ARTICLE

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A phase I/II study of nedaplatin and 5-fluorouracil with concurrent radiotherapy in patients with esophageal cancer

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Abstract *Purpose*: To determine the recommended dose (RD) of cis-diammine-glycolatoplatinum (nedaplatin) when given concurrently with 5-FU and high dose radiation therapy in the treatment of esophageal cancer. The purpose of the phase II trial is to determine efficacy and further define the side effect profile. *Methods*: Twenty-six patients with clinical stage I to IVA squamous cell carcinoma of the esophagus were enrolled in a non-surgical treatment comprised of a fixed dose of fluorouracil (400 mg/m^2 administered as continuous intravenous infusion on days 1–5 and days 8–12) plus escalating doses of nedaplatin (40 mg/m^2 in level 1, 50 mg/m^2 in level 2, or 60 mg/m^2 in level 3 on days 1 and 8), repeated twice every 3 weeks with concurrent radiotherapy (60 Gy). *Results*: Between July 1998 and February 2004, a total of 26 patients entered this trial, all of whom were considered evaluable for toxicity assessment. In phase I of the study, 12 patients were treated in sequential cohorts of three to six patients per dose level. The maximum tolerated dose was reached at level 3 with two grade 4 neutropenia and one grade 4 thrombocytopenia. Thus, the recommended dosing schedule is level 2. Of the 20 patients treated at the RD level 2, including 6 patients of the RD phase I portion, 8 out of 20 patients (40%) had grade 3–4 neutropenia, 5 patients (25.0%) had grade 3–4 thrombocytopenia, 4 patients (20.0%) had grade 3 anemia and 4 patients (20.0%) had grade 3–4 esophagitis. Other toxicities were relatively mild and usually of grade 2 or less. Objective responses were noted in the 26 patients (overall response rate, 88.5%) including 11 (42.3%) complete remissions. The 1- and 3-year survival rates were 65.1 and 37.2%, respectively, with a median survival time of 21.2 months. *Conclusions*: The combination of nedaplatin and 5-FU with radiation is a feasible regimen that shows promising antitumor activity with an acceptable safety profile in patients with esophageal cancer.

Keywords Nedaplatin · Esophageal cancer · Chemoradiotherapy

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Introduction

Esophageal cancer is highly malignant. In the USA, 14,520 new cases of esophageal cancer were diagnosed in 2005, more than 90% (13,570) of which were fatal, comprising 2.4% of all cancer deaths [1]. In Japan, with at least 10,000 new cases being discovered every year, it now accounts for 3.4% of cancer deaths and is the sixth leading cause of cancer death among Japanese males. However, treatment for patients with esophageal cancer remains unsatisfactory. Although surgery is considered the standard treatment in locally advanced esophageal cancer, results of surgery remain poor, with the 5-year survival rate in the range of 5–30% [2]. Chemoradiotherapy (CRT) has revealed promising results in the treatment of esophageal cancer in the past decade. In the report of a intergroup randomized controlled trial (Radiation Therapy Oncology Group 85–01), which compared CRT with radiotherapy alone, the 5-year survival rate was 27% after CRT while after radiation therapy alone (64 Gy) was 0% [3]. Therefore, CRT became an important option in the treatment of esophageal cancer.

Cisplatin and 5-FU were the key drugs in these treatment protocols [3–8]. However, it has been reported that cisplatin-based chemotherapy often produces substantial toxicity, including nephrotoxicity and gastrointestinal toxicity, requiring frequent modifications of the treatment, and these toxicity levels increase when combined with radiotherapy [9]. Therefore, there is a need to identify a new combination with a drug that is less toxic than CDDP or a drug that can provide better therapeutic results with reduced adverse reactions. Several platinum complexes have been synthesized such as Cis-diammine-glycolatoplatinum (nedaplatin, CDGP). Nedaplatin combines with DNA, interfering with its duplication, similarly to the way CDDP does. It is now marketed in Japan as a drug with an antitumor activity comparable to that of cisplatin [10], with less renal toxicity due to its property of being approximately ten times as soluble in water as CDDP [11, 12]. A phase I study against various advanced cancers demonstrated the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II studies of nedaplatin were 120 and 100 mg/m^2 every 4 weeks, respectively, and dose-limiting toxicity (DLT) was evidenced by thrombocytopenia; no severe renal or gastrointestinal toxicities were observed [13]. Nedaplatin produced promising response rates in phase II trials for treatment of squamous cell carcinoma (SCC) of the head and neck [14], lung [15], uterus cervix [16] and esophagus [17]. However, it is still inconclusive whether nedaplatin could replace cisplatin for the treatment of esophageal cancer since phase III trails have not been performed to allow direct comparison of nedaplatin to CDDP.

A combination of nedaplatin and 5-FU resulted in the synergistically enhanced inhibition of tumor growth seen in the combination of cisplatin and 5-FU in a preclinical murine tumor model [18]. In a clinical study, combination chemotherapy using nedaplatin and 5-FU has been reported to be a safe and effective regimen for treating advanced esophageal cancer with an overall response rate of 50% [19].

To date, there have been few reports of CRT using nedaplatin and 5-FU for both primary and preoperative therapy of esophageal cancer, each of which used a different dosing schedule [20–22]. In addition, none of these reports include a phase I dose escalation study. We therefore have conducted this phase I/II study to determine the MTD of nedaplatin and to evaluate its efficacy when administered in combination with 5-FU to patients with esophageal cancer as part of the CRT treatment.

Patients and methods

Eligibility

Patient were considered eligible for this study based on the following criteria: histologically proven esophageal cancer; clinical stage I to IVA (International Union Against Cancer tumor-node-metastasis system, 1997); no prior radiation therapy or chemotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; age 20–78 years; adequate baseline bone marrow function (hemoglobin level 9 g/dl, white blood cell count $>4{,}000/mm^3$ and $<10{,}000/mm^3$, neutrophil count $>2{,}000/mm^3$ and platelet count $>100{,}000/mm^3$); adequate hepatic function (total bilirubin level 1.5 mg/dl and aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase levels 2.0× the upper limit of normal); adequate renal function (serum creatinine level 1.5 mg/dl); adequate respiratory and cardiac function (PaO_2 60 mmHg, normal ECG); and a life expectancy of at least 2 months. Patients were excluded from the study for the presence of any of the following: active concomitant malignancy; tracheoesophageal fistula; serious complications (severe heart disease, pulmonary fibrosis, interstitial pneumonitis or a tendency to bleeding); history of drug hypersensitivity; pregnant or lactating females. Written informed consent was obtained from all patients. This study was approved by the review boards at our institution.

Pretreatment evaluation

The extent of disease evaluation included barium esophagography, esophagoscopy and cervical, chest and abdominal computed tomography (CT) scans. The T-factor in patients with less than T4 was determined by endoscopic ultrasound of the esophagus (if technically possible). Bronchoscopy was performed for cervical or mid-esophageal tumors. Positive lymph nodes were defined as being ≥1 cm on any of the images.

Treatment protocol

Treatment consisted of two cycles of nedaplatin (Shionogi Co Ltd, Osaka, Japan; nedaplatin doses were escalated to 40, 50, or 60 mg/m^2 in subsequent cohorts) on days 1 and 8 and continuous infusion of 5-FU 400 mg/m^2/day on days 1–5 and on days 8–12, repeated twice every 3 weeks, with concurrent radiotherapy (60 Gy) in 30 fractions over 6 weeks. Nedaplatin was diluted in 500 ml saline and infused over a period of 2 h. 5-FU was diluted in saline (250 mg/500 ml saline) and drip-infused continuously over a period of 120 h. Concomitant medications routinely administered before nedaplatin administration included 8 mg ondansetron plus 8 mg dexamethasone, both given intravenously. Radiation therapy was started on day 1 concomitantly with chemotherapy and was delivered with megavoltage equipment using anterior–posterior opposed fields up to 46 Gy to the primary tumor, the metastatic lymph nodes and the regional nodes. A boost dose of 14 Gy was given to the primary tumor and to the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique or multiple fields. The clinical target volume for the

primary tumor was defined as the gross tumor volume plus 3 cm craniocaudally. The planning target volumes for the primary tumor and the metastatic lymph nodes were determined with 1.0–1.5 cm margins to compensate for setup variations and internal organ motion. The radiation dose to the spinal cord was kept at a maximum of 50 Gy. During the treatment, a complete blood count, including differential and serum chemistry, and urinalysis were performed at least twice a week.

Study design

In phase I of the study, three patients were initially enrolled at each dose level. If none of the patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If one of the three patients experienced DLT, then three additional patients were enrolled at the same dose level. If two or more DLTs occurred at a given dose level, that level was considered to be the MTD and the dose escalation had to be stopped. The RD for phase II trials was defined as the dose preceding the MTD. DLT was defined as the occurrence of any one of the following during treatment: Grade 4 neutropenia lasting more than 7 days, any febrile neutropenia, grade 4 thrombocytopenia, grade 3 nonhematologic toxicity lasting more than 7 days or grade 4 nonhematologic toxicity. Any event resulting in treatment discontinuation for longer than 2 weeks was also considered to be a DLT. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI–CTC), version 2.0. CRT was interrupted in the face of grade 4 hematological toxicity or febrile grade 3 or 4 neutropenia, and resumed with 25% reduction in doses of 5FU and nedaplatin if symptoms resolved to grade 2 or less. If grade 4 esophagitis occurred, CRT or radiaton was interrupted until it resolved to grade 3. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not given with the treatment. However, when grade 4 neutropenia more than 7 days or febrile neutropenia was noted, CRT was interrupted, and 50 mg/m^2/day of G-CSF was optionally given subcutaneously starting the following day and continued until symptoms recovered to grade 2. Any patient who required more than 4 weeks for recovery of adverse reactions was taken off the study.

Evaluation

The primary end-point of this trial was to evaluate the frequency of DLT, and the secondary end-point was to evaluate the potential antitumor activity. Within 4–8 weeks from the completion of CRT, upper endoscopy (with biopsy as clinically indicated), barium esophagraphy and chest and abdominal CT were performed. Response of the primary tumor was evaluated by modified criteria of the Japanese Society for Esophageal Diseases [23]. In brief, CR for the primary tumor was considered attained when endoscopy showed no visible tumors and biopsies proved negative for at least 4 weeks. PR was assigned if the primary tumor was observed on esophagography as being reduced in area by ≥50%. Progressive disease was considered to be an increase of ≥25% in the area of the tumor. Responses of the metastatic lymph nodes were assessed using the World Health Organization response criteria for measurable diseases. An independent review committee confirmed the observed responses by radiological and endoscopic examinations. Patients were evaluated every 2 months for the first 2 years after treatment and then twice a year. Upper endoscopy and chest and abdominal CT were performed every 4 months for 2 years and annually thereafter. Overall survival was defined as the time from the start of treatment until death from any cause. The distribution of time to death from date of study entry was estimated using the Kaplan–Meier product-limit method.

Results

Patient characteristics

Between July 1998 and February 2004, a total of 26 patients entered this trial, all of whom were considered evaluable for toxicity assessment. In phase I of the study, 12 patients were treated in sequential cohorts of 3–6 patients per dose level. After the MTD was defined, 14 additional patients were enrolled to confirm the suitability of this RD in phase II of the study. All patients were assessable for both toxicity and response. A summary of patient characteristics is given in Table 1. There were 6 female and 20 male patients, and their median age was 63 years. Only one patient had a WHO performance status of 2, and the remaining patients had good performance status. The majority of patients had tumors of the mid thoracic esophagus (14/26:53.8%). All patients had histologically proven SCC. Forty-six percent of the patients were diagnosed as being in stage IVA. The characteristics of both phases before treatment were similar.

DLTs and recommended dose level

Twelve patients were enrolled in phase I of the study and were administered three dose levels of nedaplatin combined with 5-FU 400 mg/m^2 and concurrent radiotherapy (60 Gy). The various dose levels, the number of patients and the DLTs which were observed during the CRT in determination of MTD are summarized in Table 2. At the starting dose (level 1) of nedaplatin (40 mg/m^2), no grade 3 or 4 toxicity was observed in the three patients treated. At level 2 of nedaplatin (50 mg/m^2), one of the first three patients developed grade 4 neutropenia which continued for more than 7 days during treatment, thus an additional three patients were recruited for the same dose level. No DLTs occurred among these last patients. Dose level 3 of nedaplatin

Table 1 Patients characteristics

Nedaplatin (mg/m^2)	Phase I portion			Phase II portion	Total
	40	50	60	50	
No. of patients	3	6	3	14	
Age years					
Median	64	67.3	57	62.3	63.0
(Range)	(54–76)	(60–72)	(53–61)	(51–68)	(51–76)
Male/female	3/0	5/1	1/2	11/3	20/6
Performance status					
PS 0	2	6	2	9	19
PS 1	1	0	1	4	6
PS 2	0	0	0	1	1
Tumor location					
Proximal	0	1	1	3	5
Middle	2	4	1	7	14
Distal	1	1	1	4	7
Tumor[a]					
1	1	0	0	3	4
2	0	1	0	2	3
3	1	4	2	3	10
4	1	1	1	6	9
Node[a]					
0	1	1	0	5	7
1	2	5	3	9	19
Metastasis [a]					
0	2	4	1	7	14
1a	1	2	2	7	12
Clinical stage					
I	1	0	0	3	4
II	0	1	0	2	3
III	1	3	1	2	7
IVA	1	2	2	7	12

[a]Numbers correspond to the tumor-node-metastasis system of classification. (UICC1997)

Table 2 Results of dose escalation

Dose level	Nedaplatin (mg/m^2)	No. of patients	Type of DLTs (no of patients)
1	40	3	None
2	50	6	Neutropenia (l)
3	60	3	Neutropenia (2) Thrombocytcpcnia (1)

DLT Dose-limiting toxicity

(60 mg/m^2) constituted the toxic dose, with 3 of 3 patients experiencing DLT. The first patient had grade 4 neutropenia for more than 7 days plus grade 3 thrombocytopenia. The second had grade 4 neutropenia for more than 7 days plus grade 3 anemia. The third patient, who had T4 disease, experienced grade 4 thrombocytopenia (concurrently with grade 3 neutropenia) plus grade 3 esophagitis for less than 1 week (the latter toxicity did not result in a DLT). Therefore, this dose level was identified as the MTD for this study. We concluded that dose level 2 should be considered as the RD for further study.

Safety profile

All 26 patients were assessable for toxicity. Table 3 lists the treatment-related clinical adverse events experienced by patients treated at each dose level throughout the treatment period. A separated analysis of the data from 20 patients treated at RD level 2 (6 patients accrued during phase I plus 14 additional patients from phase II) was also performed. Major treatment toxicities included myelosuppression and esophagitis. Grade 3–4 neutropenia was recorded in 11 of 26 patients (42.3%). Of the 20 patients treated at the RD, 8 (40.0%) patients experienced grade 3–4 neutropenia. Grade 3–4 thrombocytopenia was observed in 7 of 26 patients (26.9%), with 5 patients (25.0%) presenting with grade 3–4 toxicity at RD. Grade 3 anemia was detected in five patients (19.2%) with no patients experiencing grade 4. Of the 20 patients treated at the RD, 4 (20.0%) patients experienced grade 3 anemia. Non-hematological side effects were manageable. Esophagitis was observed in 14 of 26 patients (53.8%). However, at RD level 2, severe esophagitis (grade 3–4) was observed in only four patients (20.0%, three patients were grade 3, one patient was grade 4), who had T4 disease. One patient with grade 4 esophagitis required transient TPN support for 1 week but completed protocol radiotherapy. Nausea developed in 53.8% (14/26) of patients, but there were no cases of grade 3 nausea. Other treatment-associated symptoms were infrequent or negligible, and it is noteworthy that no patients experienced grade 3–4 renal dysfunction. There was no treatment-related death that occurred during CRT. All patients received the full planned RT dose (60 Gy). Treatment was interrupted

Table 3 Toxicity occurring in patients throughout the study period by dose level

Dose level (Nedaplatin)	Phase I									Phase II			All patients ($n=26$)		
	1 (40 mg/m^2, $n=3$)			2 (50 mg/m^2, $n=6$)			3 (60 mg/m^2, $n=3$)			2 (50 mg/m^2, $n=14$)					
Toxicity/grade	G1 or 2	G3	G4	G1 or 2	G3	G4	G1 or 2	G3	G4	G1 or 2	G3	G4	G1 or 2	G3	G4
Neutropenia	3	0	0	4	1	1	0	1	2	7	4	2	14	6	5
Anemia	2	0	0	2	1	0	2	1	0	3	3	0	9	5	0
Thrombocytopenia	2	0	0	2	1	0	1	1	1	3	4	0	8	6	1
Nausea	2	0	–	4	0	–	2	0	–	6	0	–	14	0	–
Diarrhea	0	0	0	0	0	0	2	0	0	2	0	0	4	0	0
Mucositis	0	0	0	1	0	0	1	0	0	3	0	0	5	0	0
Esophagitis	1	0	0	2	1	0	1	1	0	5	2	1	9	4	1
Renal	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Fatigue	1	0	0	2	0	0	2	0	0	4	0	0	9	0	0
Hepatic	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0

during the CRT in 4 (20.0%) of the 20 patients, three for persistent neutropenia (within 10 days) and one for persistent grade 4 esophagitis (12 days). All of these events occurred during the second course of CRT.

Response to therapy

All patients were available for response assessment. As shown in Table 4, the overall response rate was 88.5%, including 11 complete remissions (CR; 42.3%) and 12 partial remissions (PR; 46.2%). Two (22.2%) of nine patients with T4 disease had a CR. Of the patients treated at RD, 18 of 20 patients (90%) responded to treatment, including 9 CR (45%). At the time of this report, the median survival time (MST) was 21.2 months, and the 1- and 3-year overall survival rates were 65.1 and 37.2%, respectively (Fig. 1).

Discussion

Nedaplatin, an analogue of cisplatin, is an attractive candidate for use in combination with 5-FU as it is lower in toxicity than cisplatin yet equally or more effective. Therefore, we aimed to determine the MTD of nedaplatin and assess its safety and efficacy in combination with 5-FU in patients with esophageal cancer in the CRT setting. Possibly the most widely used regimen for CRT therapy for localized esophageal cancer is that used in two landmark trials, RTOG 85-01 and INT 0123, which utilize a standard radiotherapeutic dose of 50.4 Gy or a standard course of chemotherapy which would involve two cycles of concurrent therapy followed by two cycles of adjuvant therapy [3, 5, 8]. However, our study consisted of four cycles of concurrent therapy along with a high dose of 60 Gy irradiation, the aim of which was to enhance the radiosensitization effect and conserve the antitumor effect in esophageal cancer with concurrent CRT, rather than sequential CRT [24]. In fact, a retrospective Japanese study [25] of definitive CRT consisting of 60 Gy irradiation along with four cycles of concurrent therapy of CDDP and 5-FU produced an overall radiologic CR rate of 56% and a 5-year survival rate of 29%, comparable with surgery. The dose levels of nedaplatin were set at 40, 50, and 60 mg/m^2 once per week based on the approved dosage for use in Japan being 100 mg/m^2 per course given as a 1-h intravenous infusion every 4 weeks [17].

Table 4 Response rate

	N	CR	PR	NC	PD	Response rate (%)
Total						
Stage I	4	4	0	0	0	100.0
Stage II	4	3	1	0	0	100.0
Stage III	6	2	4	0	0	100.0
Stage IVA	12	2	7	2	1	75.0
Overall	26	11	12	2	1	88.5
RD						
Stage I	3	3	0	0	0	100.0
Stage II	3	3	0	0	0	100.0
Stage III	5	2	2	1	0	100.0
Stage IVA	9	1	7	1	0	88.9
Overall	20	9	9	2	0	90.0

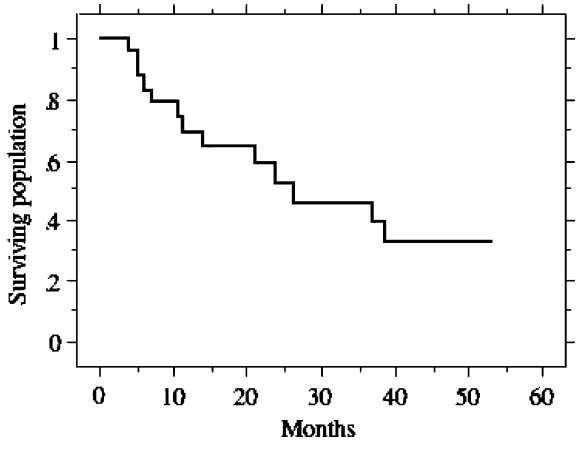

Fig. 1 Overall survival data for all patients

Phase I of this study has demonstrated the recommended dosing (RD) of nedaplatin to be 50 mg/m^2 on days 1 and 8 in combination with 5-FU at 400 mg/m^2/day on days 1–5 and days 8–12, repeated twice every 3 weeks with concurrent radiotherapy (60 Gy). The DLT associated with this regimen was hematological toxicity, consisting of neutropenia and thrombopenia. However, at RD, grade 4 leukopenia lasting for more than 7 days were observed only in three patients and improved rapidly (within 3 days) after the administration of G-CSF. Similarly, grade 4 thrombocytopenia was observed in only one patient at dose level 3, whereas no grade 4 thrombocytopenia was observed at the RD. With regard to the non-hematological toxicity, the present study generally presented with mild symptoms. Grade 4 esophagitis was only observed in one patient, who was dosed at RD, and was manageable. Four (44.4%) of nine patients who had T4 disease experienced grade 3–4 esophagitis, while non-T4 patients had no severe esophagitis. This is because the volume of tissue irradiated will vary greatly between stages I and IVA patients, leading to a much different risk of radiation induced toxicity.

In the RTOG85-01 trial, CRT was associated with 44 and 20% grade 3 and 4 acute toxicities, respectively, mostly neutropenia and esophagitis. Other 5-FU and cisplatin-based regimens have also been associated with significant toxicities [26]. In fact, with regard to hematological toxicity, Ishikura et al. [25] reported that grade 3 or higher leukopenia, anemia and thrombopenia were observed in 43, 23 and 18% of 139 patients, respectively, treated with cisplatin plus 5-FU and 60 Gy of radiotherapy. Toita et al. [27] reported grade 3–4 neutropenia in 30% of patients treated with CRT using cisplatin plus 5-FU. When comparing the hematological toxicity to our study at RD, the incidence was roughly the same but with manageable hematologic toxicity. In the RTOG 85-01 trial, grade 3 or 4 esophagitis occurred in 33% of patients receiving CRT, compared with 18% in those receiving radiotherapy alone [6]. However, the current treatment was associated with a 20% rate of esophagitis at RD, despite the higher RT dose delivered. This was consistent with the results of other Western trails [28, 29] and a Japanese phase 2 study (66.7% of T4 tumor) [30] which employed a total RT dose of ≥60 Gy. Because of the difference of study design and the relatively small number of enrolled patients, comparison of the toxicity data of this study to those of the RTOG 85-01 may be difficult. Nephrotoxicity was not specifically noted in the RTOG 85-01 trial, so it is difficult to compare the toxicity seen in this trial with that landmark trial, but given the lack of nephrotoxicity seen with nedaplatin, it certainly exhibits safety for that endpoint.

Among several different nedaplatin-based CRT regimens [20–22], grade 3–4 leukocytopenia or thrombocytopenia were found in 15.4–25.0 and 7.7–11.7% of patients, respectively. The regimens employed in these studies used lower doses of radiation or lower dosage drug regimens than our study. This is presumed to be the cause of the greater toxicity observed during our study. Although there was a high percentage (34.6%, 9/26) of patients with T4 disease, our study achieved encouraging results with a response rate of 88.5% (including 42.3% CR), a MST of 21.2 months and 1- and 3-year overall survival rates of 65.1 and 37.2%, respectively. Of note is that our results were comparable with the reported trials of CRT using the cisplatin and 5-FU protocol, including RTOG 85-01 [8] and an INT 0123/RTOG 94-05 [5], despite the limitation of a small number of patients. Previously reported nedaplatin-based CRT regimens showed relatively good response rates of 76.5% (CR rate 11.85%) [20] and 77% (CR rate 9%) [22]. Nemoto et al. [21] performed one or two cycles of treatment with nedaplatin (median dose 65 mg/m^2) and 5-FU (median dose 507 mg/m^2/24 h, 5-day continuous infusion) with radiation therapy (60–70 Gy) and reported a response rate of 94% (16/17; CR rate 41%) in spite of the low-dose regimen in which the total dose of the agents was half or less than that used in our study. However, their study involved fewer patients with T4 disease (2/17, 11.8%) than our study (34.6%).

In conclusion, this phase I/II study has demonstrated the feasibility of administering combined therapy with nedaplatin, 5-FU and radiation and has shown evidence of anti-tumor activity with an acceptable safety profile.

Conflict of interest statement

None declared.

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