Cancer Chemother Pharmacol (2009) 64:327–333
DOI 10.1007/s00280-008-0874-8

ORIGINAL ARTICLE

Phase II evaluation of nedaplatin and paclitaxel in patients with metastatic esophageal carcinoma

Youling Gong · Li Ren · Lin Zhou · Jiang Zhu · Meijuan Huang · Xiaojuan Zhou · Jin Wang · You Lu · Mei Hou · Yuquan Wei

Received: 15 August 2008 / Accepted: 7 November 2008 / Published online: 2 December 2008

Abstract
Purpose To evaluate the efficiency and toxicities of nedaplatin and paclitaxel in patients with metastatic carcinoma of the esophagus.
Methods Thirty-nine untreated patients with confirmed metastatic tumors were enrolled. Patients were treated with nedaplatin 80 mg/m^2 and paclitaxel 175 mg/m^2 on day 1. Treatment was repeated every 21 days.
Results Thirty-six patients were eligible to be evaluated to have had a response. The overall response rate was 43.6% (17/39), with complete response and partial response rates of 2.6 and 41%, respectively. The median progression-free survival and overall survival time was 6.1 and 10.3 months, respectively. Grade 3/4 toxicities were only observed in six patients [neutropenia in three patients (7.7%) and nausea/vomiting in three patients (7.7%)].
Conclusion Comparing to other regimens, combination of nedaplatin and paclitaxel achieved an encouraging clinical outcome, with relatively minimal toxicities for patients with metastatic esophageal carcinoma.

Keywords Metastasis · Esophageal carcinoma · Nedaplatin · Paclitaxel

Y. Gong and L. Ren contributed equally to this work.

Y. Gong · L. Ren (✉) · L. Zhou · J. Zhu · M. Huang · X. Zhou · J. Wang · Y. Lu · M. Hou
Department of Thoracic Oncology, Tumor Center, West China Hospital, Sichuan University, 610041 Chengdu, People's Republic of China
e-mail: renlihx@163.com

Y. Gong · Y. Lu · Y. Wei
State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, 610041 Chengdu, People's Republic of China

Introduction

The incidence of esophageal carcinoma is increasing worldwide as well as in China. Overt and incurable metastatic disease is present at diagnosis in 50% of patients, and these patients have a particularly poor prognosis. The overall 5-year survival rate for patients with newly diagnosed esophageal cancer is under 10% [11]. The median survival of patients with metastatic esophageal carcinoma is only 3–8 months [22]. Chemotherapy, which is one of the most effective treatment so far is used as part of combined modality therapy as a palliative treatment for metastatic diseases.

Recently, paclitaxel, a new broad-spectrum cytotoxic antineoplastic, has shown some promising responses against digestive tract cancer. As a single agent, paclitaxel has been shown to achieve a response rate of 32% in esophageal cancer and gastroesophageal junction cancer [1]. In addition, several Phase I/II studies have demonstrated that paclitaxel-based regimens have significant activity in patients with locally advanced and metastatic esophageal cancer [4, 6, 10, 19, 23]. However, toxicity for combination therapy was significant and included severe myelosuppression, gastrointestinal (GI) and neurologic toxicity, and a significant rate of hospitalization for treatment-related complications. So, trials have been design to develop new combination treatments that could achieve similar outcome and induce relatively minimal toxicities.

Nedaplatin (*cis*-diammine-glycolate platinum, NDP) is a second-generation platinum derivative developed in Japan, and several in vitro studies have demonstrated that nedaplatin has equivalent antitumor activity to cisplatin, with less nephrotoxity [2, 13]. Consistent with the results of the in vitro studies, recent phase I trails of nedaplatin in combination with other agents has shown modest antitumor activity

for several human tumors, with less nephrotoxicity and GI toxicity [14, 15, 18]. These reports prompted us to use a combination of nedaplatin and paclitaxel as new regimen in patients with metastatic esophageal carcinoma, because these patients have poorer tolerance systematic chemotherapy, and a less toxic treatment is desirable.

To evaluate the efficacy and toxicities of such treatment, we therefore conducted a phase II study of a combined nedaplatin-paclitaxel regimen in 39 cases of metastatic esophageal carcinoma.

Patients and methods

Study design

This was an institutional, single-arm phase II study evaluating the efficacy and toxicities of nedaplatin and paclitaxel in patients with metastatic esophageal carcinoma who had no previous treatment. The primary end point was response to treatment. Secondary end points were toxicity, PFS and OS. Patients were recruited between November 2002 and August 2006. Analysis of data took place on May 2008. All patients gave their informed consent before treatment, which was also approved by the Ethics Committee of our hospital.

Eligibility criteria

Patients were considered eligible if they had pathologic confirmation of metastatic carcinoma of the esophagus. No prior chemotherapy was allowed. Limited prior radiotherapy was allowed but those treated for the pelvis, lumbar, or thoracic spine, or those with measurable or assessable lesions who had undergone radiation therapy were excluded from the study. Patients ranged between 35 and 68 years old. Patients were required an Eastern Cooperative Oncology Group performance status of 0–2 and a life expectancy of at least 3 months. Patients were required to have dimensionally measurable disease, with an objective measurable focus: preferably the use of spiral computed tomography (CT) and measurements of maximum diameter $\geq$1 cm. Adequately defined hematological, renal, and hepatic function were required [hemoglobin $\geq$90 g/L, neutrophils $\geq 1.5 \times 10^9$/L, platelets count $\geq 100 \times 10^9$/L, creatinine $\leq$1.5 times upper limit of normal value (ULN), total serum bilirubin level $\leq$1.5 ULN and alanine aminotransferase (ALT) < 2.5 ULN ($\leq$5 times ULN if liver metastasis was present)]. The baseline examination imaging check was completed within 14 days before the first treatment. The first clinical assessment and check was completed within 7 days before the first treatment. Objective measurable focuses must have been evaluated by CT, and surface diseases analyzed by ultrasonic tomography or surface measurements. Female patients of childbearing potential must have had a negative serum pregnancy test before enrolment, and all fertile patients had to agree to use contraception during the study.

Exclusion criteria

The exclusion criteria included the following: (1) patients allergic to paclitaxel or their excipients; (2) those with a tumor diameter of larger than 10 cm in the abdominal, and hepatic metastasis >50% of total liver area, or lung metastasis >25%; (3) only with malignant pleural effusion and/or ascites with no any specific measurable disease; (4) patients with serious complications such as active bleeding sites in GI tract, GI perforation, obstruction, jaundice, noncarcinomatous fever >38°C; (5) pregnant or nursing women, and people (male and female) at childbearing age without taking contraceptive measures; (6) AST or ALT > 1.5 × UNL and AKP > 2.5 ULN (ASAT/ALAT) > 5 ULN if there was liver metastasis; (7) patients with cerebral or piamatral metastasis; (8) symptomatic pathologic changes of peripheral nerve, NCIC-CTG standard >grade 2; (9) other serious diseases or conditions.

Treatment

Chemotherapy treatment

According to the recently published nedaplatin-based or paclitaxel-based phase I/II studies [2, 6, 13, 14, 23], the dose of nedaplatin for the first course of treatment was 80 mg/m^2 over 60 min on day 1. Paclitaxel was given on day 1 at a dose of 175 mg/m^2, infusion >2 h. Treatment was repeated every 21 days. Paclitaxel infusions preceded the administration of nedaplatin.

Treatment assessment

Evaluation of disease was carried out according to RECIST criteria [20]. A complete response (CR) was defined as the disappearance of all target lesions persisting for more than 4 weeks. A partial response (PR) was defined as a minimum of a 30% decrease in the sum of the longest diameter of target lesions persisting for more than 4 weeks. A disease was defined stable (SD) where there was neither a sufficient shrinkage to qualify for a PR nor a sufficient increase in the target lesions, and progressive (PD), when there was at least a 20% increase in the sum of the longest diameter of the target lesions or appearance of new lesions. Assessment of response was measured from spiral CT imaging every two cycles of therapy.

Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Dose modification

The dose of paclitaxel was reduced to 150 mg/m^2 if one of the following conditions occurred: grade 3 neutropenia with infection, grade 4 neutropenia, grade 3 thrombocytopenia or >grade 3 sensory neurotoxicity. If toxicity persisted, a second dose reduction of paclitaxel to 135 mg/m^2 was allowed. In cases of fatigue or asthenia above grade 3, treatment was postponed for 1 week and restarted when the patient recovered to below grade 2. Patients requiring a delay in therapy for >2 weeks or more than two dose reductions were removed from the study. A new cycle of therapy could begin if the neutrophils count were $\geq 1.5 \times 10^9$/L, the platelets count were $\geq 80 \times 10^9$/L, and all relevant nonhematological toxicities were grade ≤ 2. Once a dose had been reduced during a treatment cycle, re-escalation was not permitted during any other subsequent cycles.

Statistical methods

The statistical analysis was performed using the SPSS software (version 13.0). Descriptive variables of patient characteristics and toxicity were calculated directly from the database. The PFS was measured from the date the treatment began to the date of progression, and OS was considered from the start of treatment to date of data analysis or date of loss from follow-up for patients alive. Patients without disease progression who discontinued the study for any reason were censored at the last on study tumor assessment date. Median survival times and survival curves were estimated using the method of Kaplan-Meier analysis and were compared using a log-rank test. A value of $P < 0.05$ (2-sided) was considered with statistical significance.

Results

A total of 39 patients were recruited. Patient characteristics are shown in Table 1. Median age at diagnosis was 58 years, and most of patients was male (87.2%). The median performance status at the start of treatment was 1. Almost all patients (92.3%) had pathology of squamous-cell carcinoma (SCC), and others were adenocarcinoma (7.7%). The median follow-up time for the patients alive was 11 months (range: 3–16 months). A total of 122 treatment cycles were delivered, which amounts to a median of three cycles per patient (range: 1–6 cycles).

Response to treatment

Three patients were not evaluated for response due to inadequate treatment of one or two cycles of chemotherapy and these patients still had been included for evaluation. About 36 patients were assessed as having had a response. One patient with SCC (2.6%) showed CR; 16 patients (41%) had PR, 17 patients (43.6%) had SD, and in 2 patients (5.1%) the disease progressed. The overall response was 43.6% (17/39), all with confirmed efficacy after 4 weeks. The response rates were 44.4% (16/36) and 33.3% (1/3) for patients with SCC and adenocarcinoma, respectively. The responses to therapy are shown in Table 2.

Table 1 Patient demographics ($n = 39$)

Characteristics	Number of patients (%)
Age (years)	
Median	58
Range	35–68
Sex	
Male	34 (87.2)
Female	5 (12.8)
ECOG performance status	
0	5 (12.8)
1	23 (59.0)
2	11 (28.2)
Pathology	
Squamous-cell carcinoma	36 (92.3)
Adenocarcinoma	3 (7.7)
Differentiation	
Poor-differentiated	12 (30.8)
Moderate-well differentiated	22 (56.4)
Unknown	5 (12.8)
Metastatic sites ($n = 44$)[a]	
Lymph nodes	26 (66.7)
Liver	6 (15.4)
Bone	5 (12.8)
Other sites	7 (17.9)

[a] Five patients had two metastatic sites

Table 2 Responses to treatment ($n = 39$)

Treatment outcome	Number of patients (%)		
	Patients with SCC ($n = 36$)	Patients with adenocarcinoma ($n = 3$)	Total ($n = 39$)
CR	1 (2.8)	0	1 (2.6)
PR	15 (41.7)	1 (33.3)	16 (41.0)
CR and PR group	16 (44.4)	1 (33.3)	17 (43.6)
SD	15 (41.7)	2 (66.7)	17 (43.6)
PD	2 (5.6)	0	2 (5.1)
SD and PD group	17 (47.2)	2 (66.7)	19 (48.7)
Not evaluated	3	0	3 (7.7)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *SCC* squamous-cell carcinoma

Follow-up studies continued until May 2008, three patients who had not been evaluated for responses were lost to follow-up. The median PFS of the whole group was 6.1 months (95% CI, 5.7–6.3 months) and Kaplan-Meier curves are shown Fig. 1. The median PFS of the patients who had PR or CR (PR and CR group) was 6.4 months (95% CI, 6.1–6.5 months). In patients who had SD or PD (SD and PD group), the median PFS was 4.7 months (95% CI, 3.6–5.8 months; $P = 0.025$) (Fig. 2). The median overall survival time of all patients was 10.3 months (95% CI, 10.1–10.4 months) (Fig. 3). There was a significant difference in the median OS between the patients who had showed response versus those who had not ($P = 0.003$). Median OS was 11.3 months (95% CI, 10.8–11.8 months) for the PR and CR group and 9.2 months for the SD and PD group (95% CI, 8.2–10.2 months), respectively (Fig. 4).

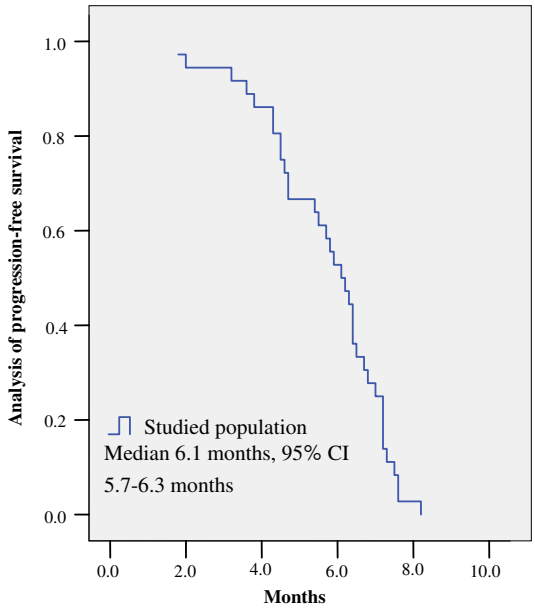

Fig. 1 Kaplan-Meier analysis of progression-free survival in the studies population

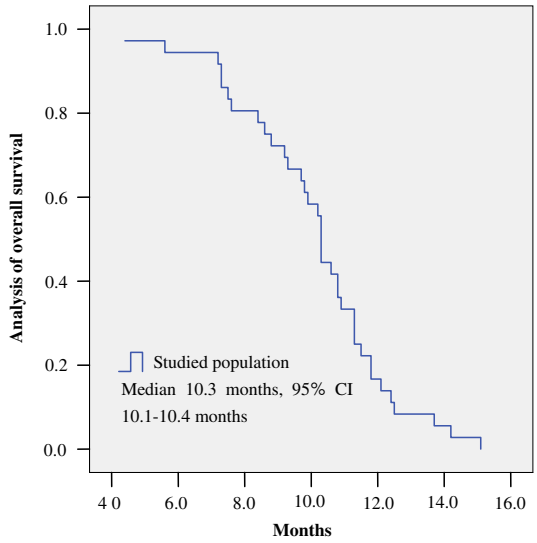

Fig. 3 Kaplan-Meier analysis of overall survival in the studies population

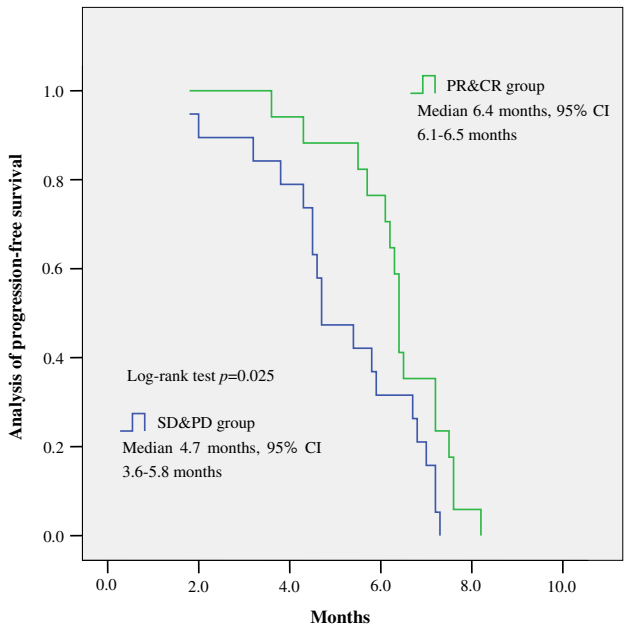

Fig. 2 Kaplan-Meier analysis of progression-free survival in the patients who had PR/CR or SD/PD

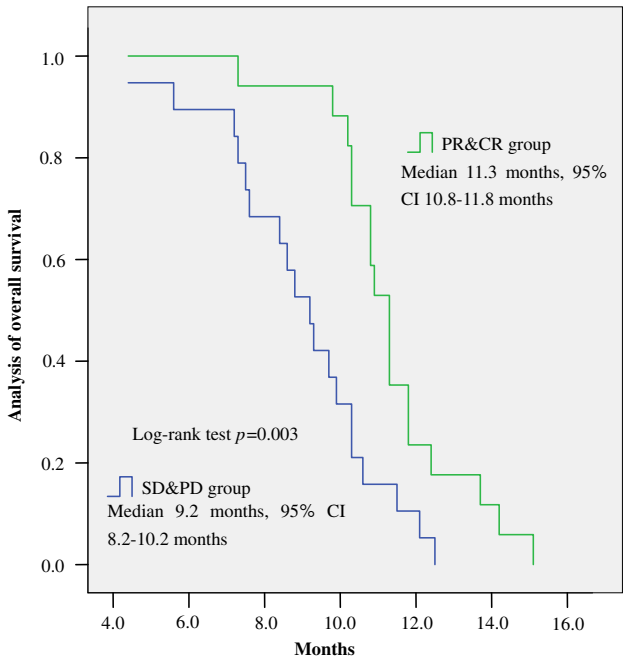

Fig. 4 Kaplan-Meier analysis of overall survival in the patients who had PR/CR or SD/PD

Treatment-related toxicities

Thirty-nine patients were evaluated for toxicity and the toxicities are summarized in Table 3. The combination of nedaplatin and paclitaxel proved to be tolerable. The most common toxicity was neutropenia and nausea. Grade 3 neutropenia and nausea/vomiting were observed in three patients (7.7%) and three patients (7.7%), respectively. Grade 3 anemia and alopecia were seen in one (2.6%) and one (2.6%) patient, respectively. The other major grade 2 toxicities included neutropenia in 22 patients (56.4%), anemia in 7 patients (17.9%), nausea in 12 patients (30.8%), vomiting in 6 patients (15.4%), and myalgia in 5 patients (12.8%), respectively. No grade 4 clinical toxicities and treatment-related deaths were recorded among all the patients. In addition, there was none of treatment-related nephrotoxicity observed in this study.

Discussion

Esophageal cancer is a common malignant tumor in the upper GI tract with very poor prognosis [11]. Researchers around the world are therefore searching for better therapies to prolong the survival and improve patient's quality of life. In present study, for the first time, combination of nedaplatin and paclitaxel has successfully shown the high activity for metastatic esophageal carcinoma. We observed an objective response rate of 43.6% and median OS of 10.3 months, respectively, with clinical acceptable toxicities.

Therapies of metastatic esophageal carcinoma still remain a serious challenge to clinical oncologists. Cisplatin and 5-FU remains the most commonly used combination and response rates reported in patients with metastatic disease are 30–35%, and the median survival is 8–9.5 months [7, 16]. However, in one randomised study performed in patients with metastatic disease, the toxicity of this regimen appeared to be severe [3]. Decades ago, several new agents such as paclitaxel and irinotecan have recently shown promising activity in the treatment of advanced or metastatic esophagus carcinoma and highlight the potential impact they may have in a combination therapy regimen for these patients.

Table 4 summaries several recently published comparative phase I and phase II trails of platinum-based or pactaxel-based conventional regimens (not included the targeting drugs, such as capecitabine) for advanced or metastatic esophageal carcinoma. As it shown, gemcitabine, paclitaxel, docetaxel, irinotecan, nedaplatin and carboplatin had been evaluated as the new regent for such patients. Polee et al. reported that paclitaxel and cisplatin introduced a relative longer median PFS of 8 months, but the median time of OS was only 9 months [19]. The highest median OS (14.6 months) was reported by Ilson and the colleagues, while the median PFS was only 4.2 months [8]. Compared to these published results, the response rate of 43.6% with the median PFS of 6.1 months and median OS of 10.3 months observed in our study is in line with the results reported in the other studies with combination regimen. In addition, the patients who had PR or CR had the significant longer time in PFS and OS than those who had only SD or PD, respectively.

Considering the performance status and chemotherapy tolerance of cancer patients in metastatic stage, treatment-related toxicities should be strictly limited. From Table 4, the most noticeable minimal toxicities were observed in bi-weekly administration of paclitaxel and cisplatin for advanced esophageal carcinoma, and there were no other grade 3 toxicities besides only grade 3/4 nausea (2%) and vomiting (6%) [19]. In present study, the most common grade 3 toxicities were neutropenia (7.7%), nausea (5.1%) and anemia (2.6%), respectively. The toxicities of nedaplatin and paclitaxel regimen were similar with the paclitaxel-based regimen reported by Zhang et al. [23] and Ilson et al. [10], and more minimal than other studies which applied gemcitabine plus cisplatin, paclitaxel plus carboplatin, nedaplatin plus docetaxel, or irinotecan plus cisplatin/cisplatin-5-fluorouracil [6, 8, 9, 12, 17, 21]. The combination of nedaplatin and paclitaxel was deemed safe in patients with metastatic esophageal carcinoma, despite the toxicity observed.

Until now, some drugs had been applied for esophageal carcinoma, such as capecitabine and oxaliplatin. Very recently, a randomized phase III trail (REAL-2) evaluated capecitabine and oxaliplatin as alternatives to infused 5-fluorouracil and cisplatin, respectively, for untreated advanced esophagogastric carcinoma [5]. The

Table 3 Treatment-related toxicities ($n = 39$)

Toxicities	Toxicity grades *n* (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Neutropenia	14 (35.9)	22 (56.4)	3 (7.7)	0
Anemia	31 (79.5)	7 (17.9)	1 (2.6)	0
Thrombocytopenia	26 (66.7)	4 (10.3)	0	0
Non-hematological				
Nausea	25 (64.1)	12 (30.8)	2 (5.1)	0
Vomiting	14 (35.9)	6 (15.4)	1 (2.6)	0
Diarrhea	8 (20.1)	4 (10.3)	0	0
Neuropathy	6 (15.4)	4 (10.3)	0	0
Myalgia	11 (28.2)	5 (12.8)	0	0
Fatigue	22 (56.4)	3 (7.7)	0	0
Alopecia	16 (41.0)	0	1 (2.6)	0
Allergic reaction	4 (10.3)	2 (5.1)	0	0

Table 4 Summaries of recently published comparative studies for advanced or metastatic esophageal carcinoma by paclitaxel or platinum-based conventional chemotherapy

Studies	Pathology	Sample	Regimen	Median PFS (months)	Median OS (months)	Several grade 3/4 toxicities (%)					
						Neutropenia	Anemia	Thrombocytopenia	Fatigue	Myalgia	Nausea
Urba [21]	Ade and Squa	64	GEM and DDP	2.9	7.3	31	11	11	8	NA	17
El-Rayes [6]	Ade and Squa	35	TAX and CBP	2.8	9	51.3	18.1	6	12.1	15.1	6.1
Zhang [23]	Squa	39	TAX and DDP	7	13	12.8	0	0	0	0	5.1
Ilson [10]	Ade and Squa	102	TAX weekly	5.7	9.1	5	9	1	NA	0	2
Ilson [8]	Ade and Squa	61	CPT-11 and 5FU and DDP	5.7	10.8	57.4	NA	NA	35	0	17
Cho [4]	Squa	32	TAX and DDP	4.8	7	19	16	0	20	NA	8
Ilson [9]	Ade and Squa	35	CPT-11 and DDP	4.2	14.6	46	31	0	3	NA	6
Polee [19]	Ade and Squa	51	TAX and DDP	8	9	0	0	0	0	0	2
Millar [17]	Ade and Squa	42	GEM and DDP	NA	11	28	3	16	31	NA	37
Kanai [12]	Ade and Squa	27	NDP and DTX	4.3	11.4	37	19	0	0	NA	0
Gong	Ade and Squa	39	NDP and TAX	6.1	10.3	7.7	2.6	0	0	0	5.1

PFS progression-free survival, *OS* overall survival, *Ade* adenocarcinoma, *Squa* squamous-cell carcinoma, *GEM* gemcitabine, *DDP* cisplatin, *CBP* carboplatin, *TAX* paclitaxel, *CPT-11* irinotecan, *NDP* nedaplatin, *5FU* 5-fluorouracil, *DTX* docetaxel, *NA* not available

more effective regimen includes epirubicin, oxaliplatin and capecitabine (EOX) achieved the median PFS of 7 months and median OS of 11.2 months, while the relative higher treatment-related toxicities were observed. So, the standard (suitable) chemotherapy for advanced or metastatic esophageal carcinoma still needs more clinical investigations.

In conclusion, combination of nedaplatin and paclitaxel is an active and promising regimen for metastatic esophageal carcinoma with response rates similar to the previous reports. Further multicenter, randomized, perspective clinical trials will enable to find better ways to combine the effective drugs for relieve treatment-related toxicities, prolong the treatment cycles and to improve the overall survival rate.

References

1. Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP (1994) Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 86:1086–1091
2. Alberts DS, Fanta PT, Running KL, Adair LP Jr, Garcia DJ, Liu-Stevens R, Salmon SE (1997) In vitro phase II comparison of the cytotoxicity of a novel platinum analog, nedaplatin (254-S), with that of cisplatin and carboplatin against fresh, human ovarian cancers. Cancer Chemother Pharmacol 39:493–497
3. Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, Bedenne L, Namer M, De Besi P, Gay F, Collette L, Sahmoud T (1997) Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 33:1216–1220
4. Cho SH, Chung IJ, Song SY, Yang DH, Byun JR, Kim YK, Lee JJ, Na KJ, Kim HJ (2005) Bi-weekly chemotherapy of paclitaxel and cisplatin in patients with metastatic or recurrent esophageal cancer. J Korean Med Sci 20:618–623
5. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR, Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
6. El-Rayes BF, Shields A, Zalupski M, Heilbrun LK, Jain V, Terry D, Ferris A, Philip PA (2004) A phase II study of carboplatin and paclitaxel in esophageal cancer. Ann Oncol 15:960–965
7. Iizuka T, Kakegawa T, Ide H, Ando N, Watanabe H, Tanaka O, Takagi I, Isono K, Ishida K, Arimori M (1992) Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japanese Esophageal Oncology Group Trial. Jpn J Clin Oncol 22:172–176
8. Ilson DH, Ajani J, Bhalla K, Forastiere A, Huang Y, Patel P, Martin L, Donegan J, Pazdur R, Reed C, Kelsen DP (1998) Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 16:1826–1834
9. Ilson DH, Saltz L, Enzinger P, Huang Y, Kornblith A, Gollub M, O'Reilly E, Schwartz G, DeGroff J, Gonzalez G, Kelsen DP (1999) Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 17:3270–3275
10. Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP (2007) Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 18:898–902

11. Jemal A, Siegel R, Ward E (2006) Cancer statistics, 2006. CA Cancer J Clin 56:106–130
12. Kanai M, Matsumoto S, Nishimura T (2007) Retrospective analysis of 27 consecutive patients treated with docetaxel/nedaplatin combination therapy as a second-line regimen for advanced esophageal cancer. Int J Clin Oncol 12:224–227
13. Kawai Y, Taniuchi S, Okahara S (2005) Relationship between cisplatin or nedaplatin-induced nephrotoxicity and renal accumulation. Biol Pharm Bull 28:1385–1388
14. Kurata T, Tamura K, Yamamoto N, Nogami T, Satoh T, Kaneda H, Nakagawa K, Fukuoka M (2004) Combination phase I study of nedaplatin and gemcitabine for advanced non-small-cell lung cancer. Br J Cancer 90:2092–2096
15. Kurita H, Yamamoto E, Nozaki S, Wada S, Furuta I, Kurashina K (2004) Multicenter phase I trial of induction chemotherapy with docetaxel and nedaplatin for oral squamous cell carcinoma. Oral Oncol 40:1000–1006
16. Levard H, Pouliquen X, Hay JM, Fingerhut A, Langlois-Zantain O, Huguier M, Lozach P, Testart J (1998) 5-Fluorouracil and cisplatin as palliative treatment of advanced oesophageal squamous cell carcinoma. A multicentre randomised controlled trial. The French associations for surgical research. Eur J Surg 164:849–857
17. Millar J, Scullin P, Morrison A, McClory B, Wall L, Cameron D, Philips H, Price A, Dunlop D, Eatock M (2005) Phase II study of gemcitabine and cisplatin in locally advanced/metastatic oesophageal cancer. Br J Cancer 93:1112–1116
18. Okuda K, Hirose T, Ishida H, Kusumoto S, Sugiyama T, Ando K, Shirai T, Ohnishi T, Horichi N, Ohmori T, Adachi M (2008) Phase I study of the combination of nedaplatin and weekly paclitaxel in patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol 61:829–835
19. Polee MB, Eskens FA, van der Burg ME, Splinter TA, Siersema PD, Tilanus HW, Verweij J, Stoter G, van der Gaast A (2002) Phase II study of bi-weekly administration of paclitaxel and cisplatin in patients with advanced oesophageal cancer. Br J Cancer 86:669–673
20. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
21. Urba SG, Chansky K, VanVeldhuizen PJ, Pluenneke RE, Benedetti JK, Macdonald JS, Abbruzzese JL, Southwest Oncology Group Study (2004) Gemcitabine and cisplatin for patients with metastatic or recurrent esophageal carcinoma: a southwest oncology study group. Invest New Grugs 22:91–97
22. Vestermark LW, Sørensen P, Pfeiffer P (2008) Chemotherapy to patients with metastatic carcinoma of the esophagus and gastroesophageal junction. A survey of a Cochrane review. Ugeskr Laeger 170:633–636
23. Zhang X, Shen L, Li J, Li Y, Li J, Jin M (2008) A phase II trial of paclitaxel and cisplatin in patients with advanced squamous-cell carcinoma of the esophagus. Am J Clin Oncol 31:29–33