

A Combined Therapy with Docetaxel and Nedaplatin for Relapsed and Metastatic Esophageal Carcinoma

HIDEO MATSUMOTO¹, YOKO HIRABAYASHI¹, HISAKO KUBOTA¹,
HARUAKI MURAKAMI¹, MASAHARU HIGASHIDA¹, KEN HARUMA²,
JUNICH HIRATSUKA³, MASAFUMI NAKAMURA¹ and TOSHIHIRO HIRAI¹

Departments of ¹Digestive Surgery, ²Gastroenterological Medicine and
³Radiology, Kawasaki Medical School, Kurashiki City, Okayama, Japan

Abstract. We performed combined chemotherapy using docetaxel and nedaplatin with and without radiation therapy as a second-line treatment for relapsed or metastatic esophageal carcinoma. Eighteen patients were enrolled from April 2003 to June 2010; 10 cases were metastatic and 8 cases were recurrent. Nedaplatin (30 mg/m²) and Docetaxel (30 mg/m²/day) were administered on days 1, 8 and 15. Nine cases undertook the combined-chemotherapy only, with a response rate of 22.2% (2/9). The other nine cases received combined chemo-radiotherapy, with a response rate of 55.5% (5/9). The median survival time of all patients was 273 days, the median survival time for patients treated with combined chemotherapy was 331 days, while for patients treated with combined chemoradiotherapy was 244 days. The two-year survival rate overall was 11.1% (1/9). The adverse event of leukocytopenia greater than grade 3 was observed in three cases of combined chemoradiotherapy cases only. Docetaxel and Nedaplatin combination chemotherapy is well tolerated and useful as second-line chemotherapy for patients with relapsed or metastatic esophageal cancer.

Esophageal squamous cell cancer is a highly aggressive form of cancer which often spreads rapidly to the regional lymph nodes and to distant organs, so that recurrence or metastasis frequently occur after curative resection or definitive chemoradiation (CRT). Recurrent and metastatic esophageal cancer is an incurable disease and patient outcomes are frequently unsatisfactory due to the lack of effective second-line therapies.

Correspondence to: Hideo Matsumoto, MD, Ph.D., Department of Digestive Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama, 701-0192, Japan. Tel: +81 864621111, Fax +81 864621199, e-mail: h-matsu@med.kawasaki-m.ac.jp

Key Words: Docetaxel, nedaplatin, esophageal cancer, second-line treatment, chemoradiation.

The standard chemotherapy regimen in CRT for esophageal cancer is a combination of cisplatin (CDDP) and 5-fluorouracil (5-FU) (1, 2). This therapy has been shown to be effective in esophageal cancer patients.

We have used the S-1 (tegafur with gimestat and otastal potassium) plus docetaxel with radiation regimen as a first-line therapy since 2006 in order to obtain a higher response rate, longer survival and less toxicity in a phase I/II trial (3). Prior to this, we had no effective regimen for patients with relapse or metastasis after the first-line treatment.

Second-line chemotherapy needs not only to be effective but also to be continued in an outpatient setting. Patient quality of life is another consideration, as the survival time is typically short. In the future, we hope to employ a platinum analogue in our second-line treatment. Cisplatin was not used in our current regimen of outpatient setting because of its nephrotoxicity and the need for multiple infusions.

Recent studies of combination-chemotherapy using nedaplatin and docetaxel as second-line chemotherapy for patients with refractory esophageal cancer showed good results (4-8). Nedaplatin is a new platinum containing analog with good anticancer properties and with both less nephrotoxicity and gastrointestinal toxicity than cisplatin (9, 10). Furthermore, it has been reported in an *in vitro* study that combination of paclitaxel with nedaplatin had a synergistic effect on lung cancer cells and was at least as effective as docetaxel plus cisplatin, and paclitaxel plus carboplatin therapies (11). Docetaxel has been reported to be effective for patients with relapsed esophageal cancer (12).

Therefore, chemotherapy with nedaplatin and docetaxel as a second-line treatment after primary chemotherapy and/or radiotherapy (RT) was performed on patients with relapsed and metastatic esophageal carcinoma. Moreover, since nedaplatin, like cisplatin, has an RT-sensitizing effect (13-16), we added RT to this combined chemotherapy in appropriate cases. The feasibility and the efficacy of this combined therapy was investigated.

Table I. Patients' characteristics.

	(N=18)
Age, years	61.6±9.9
Sex	
Male: female	17:1
Resected cases	10
Unresected cases	8
Prior therapy	
Definitive CRT	11
Adjuvant CRT	7
Prior-therapy agent	
5-FU	1
5-FU+TXT	1
S-1+TXT	14
5-FU+CDDP	2
Site of relapse/metastasis	
Esophagus	3
Lymph node	4
Pleura	3
Liver	2
Lung	2
Bone	4

CRT: Chemoradiation; 5-FU: 5-fluorouracil; TXT: Docetaxel; S-1: tegafur with gimestat and otastal potassium; CDDP: Cisplatin.

Patients and Methods

Eighteen patients with relapsed or metastatic esophageal cancer were enrolled in a second-line regimen from April 2003 to June 2010. All patients had histologically proven esophageal squamous cell carcinoma (Table I).

Eligibility was as follows: an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; adequate bone marrow function (hemoglobin level >8 g/dl; neutrophil count >1000/mm³ and platelet count >75000/mm³), adequate hepatic function (total bilirubin level <1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase levels <3× the upper limit of normal), adequate renal function (serum creatinin level <1.5mg/dl) and the absence of other active cancers. The patients provided written informed consent to receive this chemotherapy at our hospital.

Seven patients were relapsed cases and fourteen patients were metastatic cases. Nine patients underwent RT concomitantly; the metastatic site was not involved in the prior CRT area. The concomitant RT sites were as follows: lymph nodes, four patients; pleura, three patients; bone, four patients; and liver, one patient. Thirteen patients received two to four cycles, and five patients received more than five cycles of therapy (Table II).

This regimen consisted of combined nedaplatin/docetaxel (nedaplatin 30 mg/m²/day; docetaxel 30 mg/m²/day) with or without concurrent RT on days 1, 8 and 15. When RT was combined with this regimen, it was performed 5 days/weeks from weeks 1 to 3 (Table III).

Initially, docetaxel was administered intravenously at a dose of 30 mg/m² for one hour. After the docetaxel infusion, nedaplatin was administered intravenously at a dose of 30 mg/m² for two hours. Antiemetic therapy with dexamethasone (8 mg), H₂-blockers and 5-

Table II. Primary treatment and radiation.

	No. of cases (n=18)
Relapsed cases	7
Metastatic cases	11
Radiation	
With radiation	9
Without radiation	9
Radiation site	
Lymph node	4
Pleura	3
Bone	4
Liver	1
Chemotherapy cycles	
2-4	13
>5	5

hydroxy-tryptamine-3 receptor antagonists was administered intravenously before the docetaxel infusion. The proposed infusion amount was greater than 1500 ml. This regimen began as inpatient treatment and continued in an outpatient setting. In cases where the area of prior RT was not involved, RT was combined with chemotherapy, set at 45-60 Gy by the radiologist.

The cycle was repeated twice, and then its efficacy was evaluated. All the patients were evaluated every one to two months. If a beneficial effect was observed, the chemotherapy was repeated. The effect was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST v 1.0) (17). Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE v 3.0) (18).

Overall survival was measured from the treatment start date to the date of the patient's death. Time to progression (TTP) was measured from the start of treatment to the date of estimated progression according to the RECIST criteria. The Kaplan Meier method was used to estimate the overall survival time. Estimated survival times were based on the confirmation date of final survival. Statistical calculations were performed with the JMP® 8 statistical software produced by SAS Institute Inc (Cary, NC, USA). A *p*-value less than 0.05 was considered significant.

Results

Ten patients were post-CRT relapsed cases; fourteen patients were postoperative recurrent cases which had undergone the adjuvant CRT. Twenty three patients were men with a mean age of 61.6 years. Ten patients were cases of recurrence post-resection with adjuvant CRT, and fourteen patients were unresectable cases. Seventeen patients undertook definitive CRT.

The prior-chemotherapy regimens are shown in Table I. A total of eighteen cases underwent at least two cycles of therapy. Out of the nine chemotherapy-only cases, none showed complete response (CR), two showed partial response (PR), six stable disease (SD), and one showed progression of the disease (PD). The response rate of this regimen without RT was 2/9 (22.2%).

Table III. Outcome of therapy.

	Response					Response rate
	CR	PR	SD	PD	NE	
Combined chemotherapy with RT (n=9)	2	3	2	1	1	5/9 (55.5%)
Combined chemotherapy (n=9)	0	2	6	1	0	2/9 (22.2%)
Total	2	5	6	2	1	7/18 (38.8%)

CR: Complete response, PR: partial response, SD: stable disease, PD: progress disease, NE: not evaluated. Median time to progression (n=7) was 163 days (range 103 to 1217 days). Median survival time (n=18): 273 days; combined chemotherapy with RT (n=9) 235 day, combined chemotherapy cases (n=7) 171 days.

In the nine cases with RT, two showed CR, three PR, two SD, one PD, and one case was not evaluated. The response rate of the CRT was 5/9 (55.5%) (Table IV). The survival curve is shown in Figure 1.

The overall median survival time was 273 days. The median survival time for patients treated with combined chemotherapy was 331 days and for those treated with CRT was 244 days (Figure 2).

No combined-chemotherapy-only cases experienced any adverse events above grade 3. However, in the cases treated with CRT, adverse events higher than grade 3 leukocytopenia were observed in three cases (Table IV). There were no treatment-related deaths using this regimen.

Discussion

As previously reported, combination chemotherapy consisting of docetaxel and nedaplatin is an effective and safe regimen for relapsed and metastatic esophageal cancer patients. Moreover, should additional RT be compatible with chemotherapy, it is expected to offer an even more effective treatment.

Combination chemotherapy with docetaxel and nedaplatin has previously been reported as a second-line treatment (4-8). The response rate was 11 to 36.3%, and the median survival time was 5.9 to 8.5 months for this second-line treatment of combined chemotherapy using docetaxel and nedaplatin for patients with recurrent or metastatic esophageal cancer.

Our study data were similar, but the results for CRT were better. We propose that additional RT would be effective for local limited lesions. One patient with pleural metastasis survived for more than 64 months under this regimen. Moreover, as Nakajima *et al.* reported, the disease stabilization ratio (PR+PR+SD) of this regimen was 80% and good tumor dormancy effects were observed (6). The disease stabilization ratio was also high in our study. One mediastinal lymph node recurrence in a patient with SD was

Table IV. Adverse events

Combined chemotherapy with RT (n=9)

Adverse event	Grade			
	1	2	3	4
Leukocytes	1	3	3	0
Neutrophils	3	5	0	0
Platelets	4	0	0	0
Hemoglobin	3	2	0	0
Nausea	0	2	0	0
Anorexia	0	1	0	0
Fatigue	1	1	0	0

Combined chemotherapy (n=9)

	Grade			
	1	2	3	4
Leukocytes	0	3	0	0
Neutrophils	1	2	0	0
Platelets	3	0	0	0
Hemoglobin	3	1	0	0
Nausea	0	1	0	0
Anorexia	0	1	0	0
Fatigue	2	0	0	0
Alopecia	2	0	0	0

controlled for more than 12 months and the condition of another patient with lung metastasis was controlled for more than 12 months, in an outpatient setting.

We added RT to the treatment of metastatic sites, when these sites were not involved in prior CRT areas. The response rate of this group was 5/9 (55.5%), and the median survival time was 244 days. One patient who had pleural metastasis is still alive, more than three years after CRT. This CRT regimen was effective not only for controlling local lesions but also in improving patient prognosis.

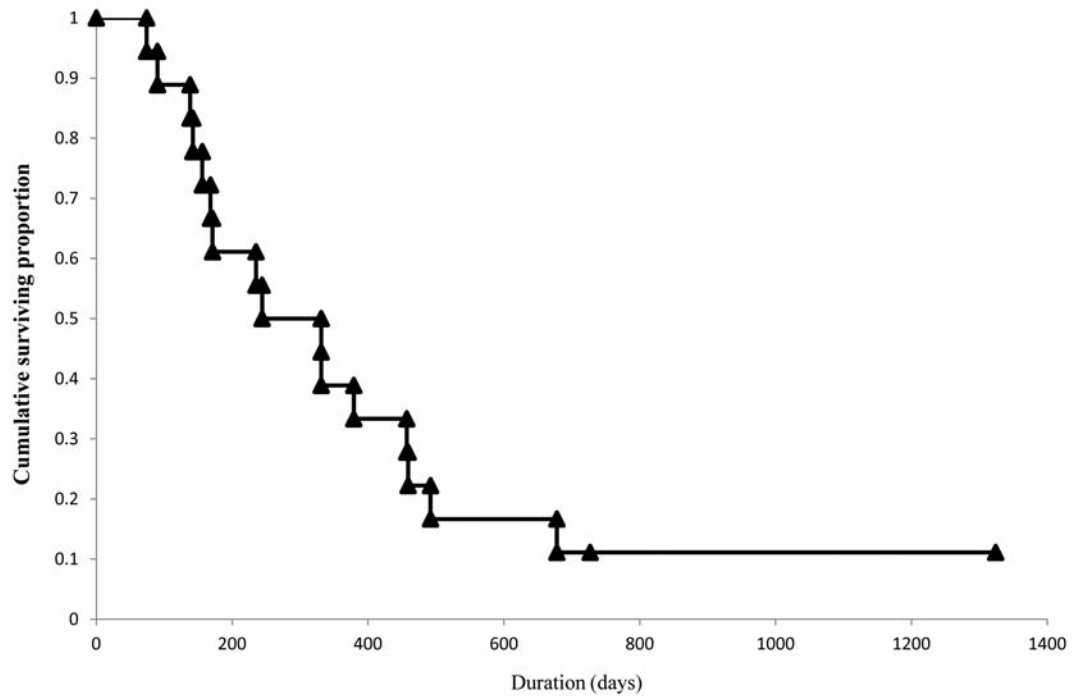


Figure 1. Survival curve for patients overall ($n=18$). The median survival time was 273 days.

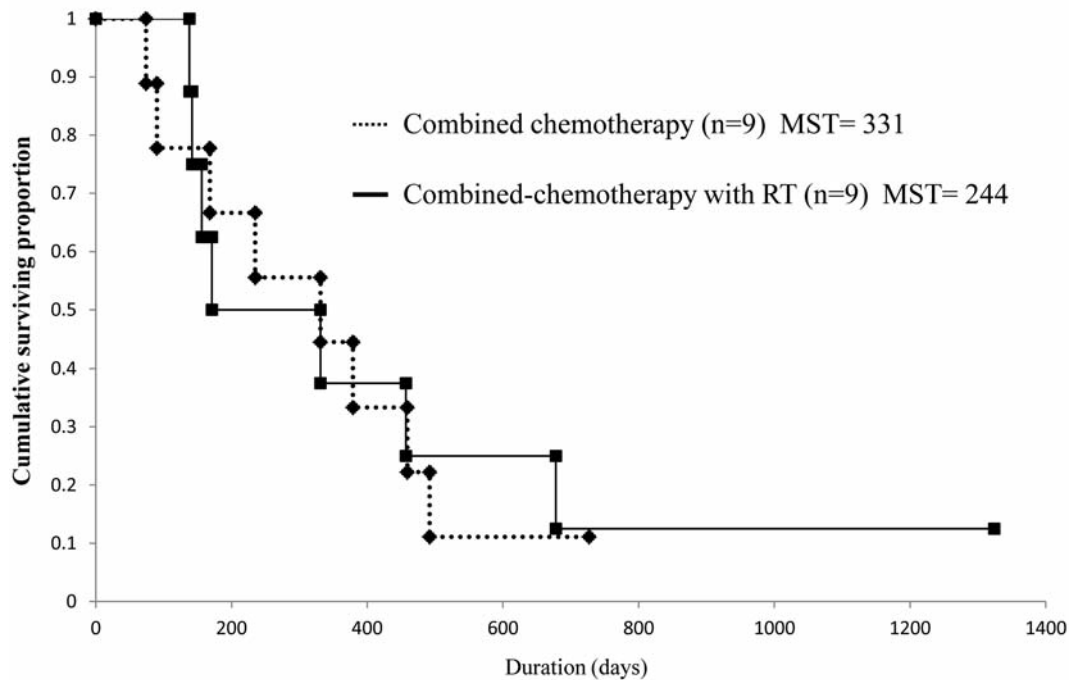


Figure 2. Survival curve for the patients treated with the combined chemotherapy and for those treated with combined chemotherapy with radiotherapy. MST: Median survival time.

In conclusion, as previously reported, docetaxel and nedaplatin combination chemotherapy is well tolerated and useful as second-line chemotherapy for patients with relapsed or metastatic esophageal cancer. Moreover, when RT is added to the regimen, it may be more effective in controlling the disease.

References

- Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, Satake M, Isikura S, Ogino T, Miyata Y, Seki S, Kaneko K and Nakamura A: Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 17: 2915-2921, 1999.
- Ishida K, Ando N, Yamamoto S, Ide K and Shinoda M: Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JCOG)/Japan Clinical Oncology Group Trial (JCOG9516). *Jpn J Clin Oncol* 34: 615-619, 2004.
- Matsumoto H, Hirai T, Hirabayashi Y, Murakami H, Higashida M and Kawabe Y: A phase I/II study of docetaxel /TS-1 with radiation for esophageal cancer patients- step1. *Jpn J Chemother* 33: 2021-2026, 2006 (in Japanese, English abstract).
- Osaka Y, Takagi S, Hoshino S, Tachibana S, Tsuchida A and Aoki T: Combination chemotherapy with docetaxel and nedaplatin for recurrent esophageal cancer in an outpatient setting. *Dis Esoph* 19: 473-476, 2006.
- Kanai M, Matsumoto S, Nishimura T, Shimada Y, Watanabe G, Kitano T, Misawa A, Ishiguro H, Yoshikawa K, Yanagihara K, Teramukai S, Mitsumori M, Chiba T, Sakai Y and Fukushima M: 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, 2007.
- Nakajima Y, Suzuki T, Haruki S, Ogiya K, Kawada K, Nishikage T, Nagai K and Kawano T: A pilot trial of docetaxel and nedaplatin in cisplatin-pretreated relapsed or refractory esophageal squamous cell cancer. *Hepatogastroenterology* 55: 1631-1635, 2008.
- Fujita Y, Hiramatsu M, Kawai M, Sumiyoshi K, Nishimura H and Takigawa N: Evaluation of combined docetaxel and nedaplatin chemotherapy for recurrent esophageal cancer compared with conventional chemotherapy using cisplatin and 5-fluorouracil: A retrospective study. *Dis Esoph* 21: 496-501, 2008.
- Jin J, Xu X, Wang F, Yan G, Liu J, Lu W, Li X, Tucker SJ, Zhong B, Cao Z and Wang D: Second-line chemotherapy with docetaxel and nedaplatin for cisplatin-pretreated refractory metastatic/recurrent esophageal squamous cell carcinoma. *J Thorac Oncol* 4: 1017-1021, 2009.
- Shiratori O, Kasai H, Uchida N, Takeda Y, Totani T and Sato K: Antitumor activity of 254-S, a platinum complex, in Rodents. *In: J. Ishigami (Ed.), recent advances in chemotherapy*, Anticancer Section, University of Tokyo Press, Tokyo pp. 635-636, 1985.
- Totani T, Aono K, Adachi Y, Komura M, Shiratori O and Sato K: Bidentate hydroxycarboxylic acid platinum(II) complexes with anti tumor activity. *In: M. Nicolini (Ed.), Platinum and other metal coordination compounds in cancer chemotherapy*, Martius Niihoff Publishing, Boston pp. 744-748, 1988.
- Uchida N, Yamada H, Yoshioka H, Maekawa R and Yoshida T: Combination therapy of paclitaxel with nedaplatin. *J New Rem Clin* 49: 478-483, 2000.
- Muro K, Hamaguchi T, Ohtsu A, Boku N, Chin K, Hyodo I, Fujita H, Takiyama W and Ohtsu T: A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. *Ann Oncol* 15: 955-959, 2004.
- Yamanaka H, Motohiro T, Miciura T, Asai A, Mori T and Koshiro H: Nedaplatin and 5-FU combined with radiation in the treatment for esophageal cancer. *Jpn J Thorac Cardiovasc Surg* 46: 943-948, 1998.
- Yoshioka T, Gamoh M, Shineha R, Ishibashi S, Shibata H, Suzuki T, Murakawa Y, Kato S, Shimodaira H, Kato S, Ishioka C and Kanamaru R: A new combination chemotherapy with cis-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for advanced esophageal cancers. *Internal Med* 38: 844-848, 1999.
- Kato H, Fukuchi M, Manda R, Nakajima M, Miyazaki T, Sohda M, Masuda N, Fukai Y, Tsukada K and Kuwano H: Efficacy and toxicity of nedaplatin and 5-FU with radiation treatment for advanced esophageal carcinomas. *Anticancer Res* 23: 3493-3498, 2003.
- Sato Y, Takayama T, Sagawa T, Okamoto T, Miyanishi K, Sato T, Araki H, Iyama S, Abe S, Murase K, Takimoto R, Nagakura H, Hareyama M, Kato J and Niitsu Y: A phase I/II study of nedaplatin and 5 fluorouracil with concurrent radiotherapy in patients with esophageal cancer. *Cancer Chemother Pharmacol* 58: 570-576, 2006.
- Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: 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(3): 205-216, 2000.
- Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN and Rubin P: CTCAE V. 3.0 development of comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 13: 176-181, 2003.

Received March 1, 2012

Revised April 2, 2012

Accepted April 3, 2012