Second-Line Combination Chemotherapy with Docetaxel and Nedaplatin for Cisplatin-Pretreated Refractory Metastatic/Recurrent Esophageal Squamous Cell Carcinoma

Jianhua Jin, MD, Xiyuan Xu, MD,† Fang Wang, MD,* Guodu Yan, MD,* Jianyue Liu, MD,‡ Wenbin Lu, MD,* Xianwen Li, MD,* Steven Jay Tucker, MD,§ Baoliang Zhong, MD,‖ Zhigang Cao, MD,¶ and Daoyuan Wang, MD#*

Background: There is an urgent need for an effective second-line chemotherapy regimen after failure of the standard cisplatin and 5-fluorouracil therapy.

Patients and Methods: This study investigated the efficacy and toxicity of the combination of docetaxel (30 mg/m^2) during a 1-hour infusion, followed by nedaplatin (50 mg/m^2) during a 2-hour infusion (both drugs were administered on day 1 as an outpatient regimen and repeated every 2 weeks) as second-line chemotherapy for patients with cisplatin-pretreated refractory metastatic/recurrent esophageal squamous cell carcinoma after surgery.

Results: Forty-six of the 48 patients (95.8%) were assessable for response. Partial response was confirmed in 13 of 48 cases yielding a response rate of 27.1% (95% confidence interval [CI], 14.5–39.7%). The median overall time to progression and overall survival was 3.1 months (95% CI, 2.3–3.9 months) and 5.9 months (95% CI, 3.9–7.8 months), respectively. The estimate of overall survival at 12 months was 16.7% (95% CI, 6.1–27.2%). Grade 3 anemia leucopenia, grade 4 anemia leucopenia and neutropenia were detected in only 4 (8.7%), 8 (17.4%), and 9 patients (19.6%), respectively.

Conclusions: The combination chemotherapy of docetaxel and nedaplatin in the outpatient setting is well tolerated and useful as second-line chemotherapy for cisplatin-pretreated refractory metastatic/recurrent esophageal squamous cell carcinoma.

Key Words: Esophageal squamous cell carcinoma, Docetaxel, Nedaplatin, Salvage chemotherapy.

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Patients with esophageal cancer generally have a poor prognosis because the majority of them already have locally unresectable or metastatic disease at presentation. Furthermore, even after surgery with curative intent, local recurrences and distant metastases are detected in approximately two thirds of the patients within 5 years of follow-up.[1] Metastatic or recurrent esophageal cancer is an incurable disease, and treatment outcomes for these patients are unsatisfactory because of the lack of effective therapies. Many patients with esophageal cancer require palliative therapy to treat symptoms, such as dysphagia. Chemotherapy is a primary option for the palliative treatment of metastatic or recurrent disease. Accordingly, it is important to develop effective and well-tolerated chemotherapeutic agents for treatment. Currently, a combination of cisplatin with continuous infusion of 5-fluorouracil (5-FU) is regarded as the reference chemotherapy regimen for metastatic or recurrent esophageal cancer, with a 30–40% response rate. However, complete responses are rare, the median duration of response is generally short (4–6 months), and the median survival is only 6–10 months.[2–7] Although a subset of patients with metastatic or recurrent esophageal cancer initially responds to this therapy, they ultimately experience a progression of disease. A number of patients who progress following first-line chemotherapy are still fit for second-line treatment. However, there is no currently established salvage treatment option.[8] There is an urgent need for an effective second-line chemotherapy regimen after failure of the standard cisplatin and 5-FU therapy.

Docetaxel has shown extensive cytotoxic activity in animal models and antitumor activity against various common cancers in clinical studies.[9,10] Clinical trials of single-

*Department of Medical Oncology, Wujin Hospital, Medical School of Jiangsu University, Changzhou, Jiangsu Province, People's Republic of China; †Department of Radiotherapy, Changzhou Cancer Hospital, Medical School of Suzhou University, Changzhou, Jiangsu Province, People's Republic of China; ‡Department of Surgery, Wujin Hospital, Medical School of Jiangsu University, Changzhou, Jiangsu Province, People's Republic of China; §Pacific Cancer Centre, Singapore, Singapore; ‖School of Public Health, Peking University, Beijing, People's Republic of China; ¶Shanghai Cancer Institute, Shanghai, People's Republic of China; and #AmMed Cancer Center, Ruijin Hospital, Medical School of Shanghai Jiaotong University, Shanghai, People's Republic of China.

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Address for correspondence: Daoyuan Wang, MD, AmMed Cancer Center, Ruijin Hospital, Medical School of Shanghai Jiaotong University, No. 197, Rui Jin Er Lu, Shanghai 200025, People's Republic of China. E-mail: ghealth2008@gmail.com

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agent docetaxel have been reported in previously treated patients with advanced esophageal cancer, with response rates ranging from 16 to 28%.[11,12] Nedaplatin (*cis*-diammine-glycolatoplatinum) is a second generation platinum that does not require hydration, several in vitro studies have demonstrated that nedaplatin has equivalent antitumor activity to cisplatin, with less nephrotoxity.[13,14] Consistent with the results of the in vitro studies, nedaplatin in combination with other agents (e.g., docetaxel) has shown modest antitumor activity for several human tumors (e.g., esophageal cancer), with less nephrotoxicity and gastrointestinal toxicity.[15–17] These reports prompted us to use a combination of docetaxel with nedaplatin as a second-line regimen in patients with advanced esophageal cancer because pretreated patients have poorer tolerance to second-line chemotherapy, and a less toxic treatment is desirable.

Accordingly, we investigated the efficacy and toxicity of the combination of docetaxel and nedaplatin as second-line chemotherapy for patients with cisplatin-pretreated refractory metastatic/recurrent esophageal squamous cell carcinoma after surgery.

PATIENTS AND METHODS

Patient Eligibility

Eligibility criteria included histologically confirmed squamous cell carcinoma of the esophagus, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and at least one measurable disease(s) as assessed by RECIST. Inclusion also required either disease progression after one or more palliative chemotherapies of cisplatin-regimen or disease recurrence within 12 months after neoadjuvant or adjuvant chemotherapy of cisplatin-regimen. Patients had to have adequate bone marrow (hemoglobin level $\geq$9 g/dl, white blood cell count $\geq$3000/mm^3, neutrophil count $\geq$1500/mm^3, and platelet count $\geq$100,000/mm^3), hepatic function (total bilirubin level $\leq$1.5 mg/dl and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels $\leq$2.5 times the upper limit of normal), and renal function (serum creatinine level $\leq$1.5 mg/dl). Minimum patient age was 18 years, and minimum life expectancy was 12 weeks. Written informed consent was obtained from all patients, and study was approved by the local ethical committees.

Exclusion Criteria

Exclusion criteria included the following: adenocarcinomas of the esophagus including gastric-esophageal junction; cerebral or leptomeningeal metastases; peripheral neuropathy grade $\geq$2 by the National Cancer Institute Common Toxicity Criteria; clinical hearing loss; active infection; active peptic ulcer disease; uncontrolled diabetes mellitus; comorbidity (congestive heart disease or angina, uncontrolled hypertension, arrhythmias, or myocardial infarction within the previous 6 months); disturbed mental state, concomitant malignancy; pregnancy, lactation, or fertility (unless using adequate contraceptives or barrier methods to prevent pregnancy) in women; and history of drug hypersensitivity.

Evaluation and Treatment

The primary end point of this study was response rate (RR), and secondary objectives were toxicity, overall survival (OS), and time to progression (TTP). All patients underwent a baseline evaluation that included a physical examination and a complete blood cell count with differential, serum chemistry analysis, esophagography, an electrocardiograph, and a computed tomography scan of the chest and other target sites. Patients received 30 mg/m^2 of docetaxel during a 1-hour infusion on day 1, followed by 50 mg/m^2 of nedaplatin during a 2-hour infusion on day 1 as an outpatient regimen and repeated every 2 weeks for six cycles. These doses were based on a phase I trial of chemotherapy using docetaxel and nedaplatin in chemotherapy-naive patients with oral squamous cell carcinoma[15] and phase I/II study for unresectable non-small cell lung cancer.[18] That phase I trial recommended 60 mg/m^2 docetaxel and 100 mg/m^2 nedaplatin every 4 weeks in chemotherapy-naive patients. Because our treatment was to be repeated every 2 weeks in patients who had had prior chemotherapy, we adjusted the doses of docetaxel and nedaplatin to 30 and 50 mg/m^2, respectively. Toxicities were assessed according to National Cancer Institute Common Toxicity Criteria (version 2.0) after each cycle. Patients were excluded if they had unacceptable toxicity, progression of the disease, or consent was withdrawn. Efficacy was evaluated every 8 weeks (four cycles) by esophagography, computed tomography scan, and/or magnetic resonance imaging. All patients who achieved complete response or partial response (PR), if applicable, continued this chemotherapy every 2 weeks as far as was possible.

Statistical Analysis

This trial used a two-stage optimal design as proposed by Simon,[19] with an 80% power to accept the hypothesis and 5% significance to reject the hypothesis. This trial was designed to detect a RR of 40% when compared with a minimal, clinically meaningful RR of 20%. Allowing for a follow-up loss rate of 10%, the total sample size was 48 patients with measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response, TTP, and survival analyses were all estimated using the Kaplan-Meier method.[20] The duration of response was defined as the interval from the onset of a complete response or PR until evidence of disease progression was found. Meanwhile, the TTP was calculated from the initiation of chemotherapy to the date of disease progression, whereas OS was measured from the initiation of chemotherapy to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, IL).

RESULTS

Patient Characteristics

From December 2004 to June 2006, a total of 48 patients were enrolled in this study from the Department of Medical Oncology, Wujin Hospital, Medical School of Jiangsu Unviersity. The characteristics of the patients are summarized in Table 1. The median age was 55 years (range,