Investigational New Drugs **20:** 95–99, 2002.

Phase II trial of docetaxel chemotherapy in patients with incurable adenocarcinoma of the esophagus

Elisabeth I. Heath[1], Susan Urba[2], John Marshall[3], Steven Piantadosi[1] and Arlene A. Forastiere[1]
[1]*Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD;* [2]*Department of Oncology, University of Michigan, Ann Arbor, MI;* [3]*Department of Oncology, Georgetown University Hospital, Washington DC, USA*

Key words: cancer of the esophagus, chemotherapy, docetaxel, paclitaxel

Summary

Background: Chemotherapy remains the primary mode of treatment for metastatic carcinoma of the esophagus. The efficacy of various chemotherapeutic regimens has been studied predominantly in patients with squamous cell carcinoma of the esophagus. In light of the increasing incidence of adenocarcinoma of the esophagus, studies evaluating newer chemotherapy agents, such as docetaxel, in this patient population are necessary. The objective of this trial was to determine the complete and partial response rate of docetaxel in patients with incurable adenocarcinoma of the esophagus.

Patients and methods: Eligible patients had histologically confirmed metastatic adenocarcinoma of the esophagus or locally extensive disease not curable with surgery or radiation therapy. Patients were either chemotherapy naive or previously treated with chemotherapy (including paclitaxel). Docetaxel was administered at a dose of 75 mg/m^2 every three weeks intravenously. Appropriate imaging studies/examinations were obtained after every two cycles to evaluate response.

Results: A total of 22 patients were enrolled in the trial. Chemotherapy-naive patients achieved a response rate of 18% (95% CI = 2.3 to 51.8) while patients who received prior chemotherapy achieved a 0% response rate (95% CI = 0 to 25). There were no complete responses. The overall median survival time is 3.4 months and the one-year survival rate is 21%. The toxicities included febrile neutropenia (32%) as well as grade 3 and 4 fatigue (14%) and anorexia (9%).

Conclusions: Although chemotherapy naive patients achieved an 18% response rate and no responses were seen in previously treated patients, the limitations of this trial does not allow for any definitive conclusions to be made about the efficacy of single agent docetaxel chemotherapy in patients with incurable esophageal cancer.

Introduction

The incidence of adenocarcinoma of the esophagus is rising [1]. Unfortunately, those diagnosed with recurrent or metastatic disease are not curable. Chemotherapeutic agents play a major role in palliative therapy and remain the primary mode of treatment. Most of the chemotherapeutic agents, such as cisplatin, 5-fluorouracil, bleomycin, and etoposide have been evaluated previously in patients with squamous cell carcinoma of the esophagus [2–4]. The majority of the trials performed were in small numbers of patients with reported response rates from 15 to 40%. The response was usually of short duration and there was no survival benefit apparent with single agent chemotherapy. Combination chemotherapy has been evaluated with slightly improved results in terms of longer duration of response (3 to 6 months), but there was still little improvement in the dismal overall survival rate. In light of the rising incidence of adenocarcinoma of the esophagus, studies evaluating newer chemotherapy agents, such as docetaxel, in this patient population are necessary.

Docetaxel is a cytotoxic antineoplastic agent which disrupts the microtubular network essential for mitotic and interphase cellular functions [5]. This semi-

synthetic compound is derived from the needles of the European yew tree, *Taxus baccata*. Docetaxel is a structurally similar compound to paclitaxel, but has a different activity profile. For example, docetaxel affects mitotic structures at the centrosome while paclitaxel affects them at the mitotic spindle. Docetaxel acts primarily during the S phase of the cell cycle versus the G2/M phase. In the P388 leukemia cell line, docetaxel has been shown to have three-fold higher intracellular concentration compared to paclitaxel and at least three times slower efflux compared to paclitaxel [6]. These differences may contribute to the higher *in vitro* anti-tumor activity observed with docetaxel compared to paclitaxel in multiple murine and human tumor cell lines, such as in gastric cancer cell lines [7].

Paclitaxel has been studied in patients with adenocarcinoma and squamous cell carcinoma of the esophagus. Ajani et al. reported a 34% and 28% response rate in paclitaxel treated patients with adenocarcinoma and squamous cell carcinoma of the esophagus, respectively [8]. These previously untreated patients who had excellent performance status experienced tolerable side effects with paclitaxel. One conclusion of the trial was that paclitaxel is an active agent against both types of esophageal cancer in previously untreated patients.

Docetaxel has been evaluated in a phase II trial of previously untreated patients with adenocarcinoma of the upper gastrointestinal tract [9]. At a dose of 100 mg/m^2 given every 3 weeks, an objective response rate of 17% was reported. Although this response rate was lower than anticipated, the majority of patients (76%) in the trial had gastric cancer, a disease also with minimal response to paclitaxel. Therefore, it is reasonable to expect a higher response rate with docetaxel in esophageal cancer patients.

The primary objective of this trial was to determine the complete and partial response rate of docetaxel in patients with incurable adenocarcinoma of the esophagus. Secondary objectives included evaluating survival time, time to tumor progression, and toxicities of docetaxel chemotherapy.

Patients and methods

Patient population

Patients with histologically confirmed adenocarcinoma of the esophagus, cardia or gastroesophageal junction were enrolled at three sites: the Johns Hopkins Oncology Center, the University of Michigan and the Georgetown University Hospital. Eligible patients with metastatic disease or locally extensive disease not curable with surgery or radiation therapy were either chemotherapy naive or previously treated with chemotherapy (including paclitaxel). Patients were greater than 18 years of age with an ECOG performance status ≤ 2.

Adequate bone marrow and hepatic function was necessary and was defined as having absolute neutrophil count (ANC) $\geq$ 1000, platelets $\geq$ 100,000, total bilirubin $<$ upper limit of normal (ULN), SGOT and/or SGPT $\leq 2.5 \times$ ULN if alkaline phosphatase is $\leq$ ULN, or alkaline phosphatase may be up to 4 $\times$ ULN if transaminases are $\leq$ ULN. Patients were not allowed to have any CNS metastasis, pre-existing peripheral neuropathy $\geq$ grade 2 and must have a life expectancy of $\geq$ 12 weeks.

Pre-treatment evaluation included signed written informed consent, complete history and physical examination, laboratory tests, CT scans of the chest, abdomen, and pelvis, EKG and urine or serum bHCG if the patient was a female of child bearing age. The study was approved by the committees for human research at all three clinical centers.

Treatment plan

Docetaxel was administered at a dose of 75 mg/m^2 every 3 weeks intravenously in the outpatient oncology clinic. One treatment every three weeks was considered one cycle. After two cycles of therapy, patients underwent follow-up CT scans of chest, abdomen, and pelvis as well as physical examination for evaluation of response. Patients were treated every three weeks until there was evidence of progression of disease, increasing side effects or a maximum of one year time period. Toxicity was graded using the NCI Common Toxicity criteria.

Criteria for response

A complete response was defined as disappearance of all clinical evidence of disease by physical examination and/or CT scan for 4 weeks. Partial response was defined as 50% or greater reduction of tumor by physical examination and/or CT scan. Size of the tumor was determined by multiplication of the two longest perpendicular diameters. Patients with no change in disease had stable disease for 4 weeks. Progressive disease was defined as a 25% or greater increase of tumor by physical examination and/or CT scan or appearance of any new lesion.

Statistical consideration

The primary objective of the study was to determine the proportion of incurable esophageal cancer patients who respond to docetaxel. The study was designed as two stage trial with a decision to continue if the response rate was 20% [10]. Enrollment would not continue if the observed response rate was $\leq 5\%$. If 1 out of the first 10 patients responded, the second stage would accrue to a total of 29 patients (80% power, 5% type 1 error). All eligible patients were included in response, toxicity and survival analyses.

Results

Patient characteristics and response

From December 1997 to September 1999, 22 patients were enrolled in the study. Patient characteristics are listed in Table 1. The mean age of patients was 61 years and the majority of patients were white males. Almost half of the patients had undergone an esophagectomy and 27% of patients received prior radiation therapy. Of the 22 patients, 11 was chemotherapy naive and the remaining 11 had prior chemotherapy, including 4 patients who had received prior paclitaxel. Forty-one percent of patients received at least 2 cycles of chemotherapy. The maximum number of cycles administered was eight. The liver and lungs were predominant sites of metastatic disease.

Chemotherapy-naive patients achieved a response rate of 18% (95% CI = 2.3 to 51.8) while patients who received prior chemotherapy achieved a 0% response rate (95% CI = 0 to 25). Overall, six patients (27%) had stable disease. There were no complete responses. The overall median survival time was 3.4 months (range 1–26 months) and the one-year survival rate was 21%. Chemotherapy naive and prior paclitaxel treated patients had a median survival time of 6 months. Patients treated with prior chemotherapy, not including paclitaxel had a median survival time of 4 months. The median time to progression was 1.4 months. To date, 2 of the 22 patients (11%) are alive with a follow-up of 28 months. These two patients were not the patients who achieved partial responses to docetaxel chemotherapy.

During the trial, the accrual rate was less than expected at 12 patients per year. Due to poor accrual, the trial was terminated prior to achieving the original sample size. In addition, to satisfy the originally planned final decision rule, 2 out of the remaining 7 patients in the trial would have had to respond. Assuming that the true response rate is 0.1, the chance of this occurring is only 15%.

Table 1. Patient characteristics

Characteristics	
Total number of patients	22
Gender	
Male	20
Female	2
Race	
White	21
Black	1
Age	61 (36–84)
Performance status	1 (0–2)
Sites of distant disease	
Liver	11
Lung	7
Lymph nodes	3
Bone	1
Prior chemotherapy	
No	11
Yes	11

Toxicity

The grade 3 and 4 toxicities included neutropenia, febrile neutropenia, fatigue, and anorexia (Table 2). Fifteen (68%) patients experienced grade 3 and 4 neutropenia. Of those patients, seven (32%) experienced febrile neutropenia requiring inpatient hospitalization. One (5%) patient experienced grade 3 peripheral neuropathy and docetaxel therapy was subsequently discontinued. This patient had received a total of eight cycles of docetaxel. Three (14%) patients experienced grade 3 and 4 fatigue and two (9%) patients experienced anorexia. There was no grade 3 and 4 nausea, vomiting, stomatitis, thrombocytopenia, or anemia.

Discussion

Previous single agent chemotherapy trials performed mainly in patients with metastatic squamous cell carcinoma of the esophagus have reported low response rates. Paclitaxel has been studied in both histologic types of cancer of the esophagus with encouraging reports of 28–34% response rates in chemotherapy naive

Table 2. Toxicity of docetaxel chemotherapy

Toxicity	Grade 3	Grade 4
	N (%)	N (%)
Neutropenia	4 (18%)	11 (50%)
Febrile neutropenia	7 (32%)	–
Peripheral neuropathy	1 (5%)	–
Fatigue	2 (9%)	1 (5%)
Anorexia	1 (5%)	1 (5%)

N = Number of patients

patients [8]. Docetaxel at 100 mg/m^2 given intravenously every 3 weeks has been studied in chemotherapy naive patients with adenocarcinoma of the upper gastrointestinal tract and the authors reported an overall 17% response rate [9]. The patients in that trial primarily had gastric cancer, but 24% of the patients had distal esophagus and gastro-esophageal junction tumors. The objectives of this current trial were to determine the complete and partial response rate of docetaxel at 75 mg/m^2 given intravenously every 3 weeks in patients with incurable adenocarcinoma of the esophagus.

The overall response rate in this trial was only 9%, with no complete responses achieved. Although the numbers were small in each group, the response rate in chemotherapy naive patients was 18% while patients with prior chemotherapy had a 0% response rate. Twenty-seven percent of all patients had stable disease. The 18% response rate in chemotherapy naive patients was similar to that reported by Einzig et al. [9].

The toxicities seen in this trial, regardless of the patient's prior chemotherapy status were acceptable. The most significant toxicity was febrile neutropenia (32%) followed by fatigue and anorexia. Docetaxel administered at the higher dose of 100 mg/m^2, 90% grade 3 and 4 neutropenia as well as 46% of febrile neutropenia were reported, necessitating future dose reductions. As anticipated, docetaxel at 75 mg/m^2 resulted in fewer toxicities than when given at a higher dose.

As a second line agent, docetaxel has been evaluated in other tumor types including lung, ovarian and breast cancer. In these trials, docetaxel generally has shown activity in paclitaxel-resistant disease. Fossella et al. treated patients with stage IIIB/IV non-small cell lung cancer with docetaxel 100 mg/m^2 or 75 mg/m^2 intravenously every 3 weeks [11]. These lung cancer patients with prior paclitaxel treatment were not stratified at enrollment, but there were approximately 40% of the patients previously treated with paclitaxel in the study. Reportedly, prior paclitaxel treatment did not affect the response or survival to docetaxel. Similarly, Kavanagh et al. concluded that docetaxel administered at 100 mg/m^2 intravenously every 3 weeks was an active second line treatment in patients with paclitaxel refractory metastatic ovarian cancer [12]. In addition, the same docetaxel dose was active in patients with paclitaxel refractory metastatic breast cancer [13]. In our study, patients who received prior taxane chemotherapy had an equivalent median survival time of 6 months compared to those who were chemotherapy naive. Although the number of patients in this trial was too few, this trend may support the hypothesis that paclitaxel and docetaxel are non-cross resistant.

Promising preclinical and clinical data has suggested greater cytotoxic potency with docetaxel compared to paclitaxel even as second line therapy. Unfortunately, the limitiations of this trial does not allow for any definitive conclusions to be made about the efficacy of single agent docetaxel in patients with incurable adenocarcinoma of the esophagus.

References

1. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr: Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 265: 1287–1289, 1991
2. Ajani JA: Contributions of chemotherapy in the treatment of carcinoma of the esophagus: results and commentary. Semin Oncol 21: 474, 1994
3. Engstrom PF, Lavin PT, Klaassen DJ: Phase II evaluation of mitomycin and cisplatin in advanced esophageal carcinoma. Cancer Treat Rep 67: 713, 1983
4. Coonley CJ, Bains M, Heelan R, Dukeman M, Kelsen DP: Phase II study of etoposide in the treatment of esophageal carcinoma. Cancer Treat Rep 67: 397, 1983
5. Bissery MC, Nohynek G, Sanderink GJ, Lavelle F: Docetaxel: A review of preclinical and clinical experience – Part I. Preclinical experience. Anticancer Drugs 6: 339–368, 1995
6. Riou JF, Naudin A, Lavelle F: Effects of Taxotere on murine and human tumor cell lines. Biochem Biophys Res Commun 187: 164–170, 1992
7. Tanaka M, Obata T, Sasaki T: Evaluation of antitumour effects of docetaxel (Taxotere) on human gastric cancers in vitro and in vivo. Eur J Cancer 32A: 226–30, 1996
8. Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP: Activity in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 86: 1086, 1994
9. Einzig AI, Neuberg D, Remick SC, Karp DD, O'Dwyer PJ, Stewart JA, Benson AB: Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal

tract previously untreated with cytotoxic chemotherapy: the Eastern Cooperative Oncology Group (ECOG) results of the protocol E1293. Med Oncol 13: 87–93, 1996
10. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10: 1–10, 1989
11. Fossella FV, DeVore R, Kerr R, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L: Phase III trial of docetaxel 100 mg/m^2 or 75 mg/m^2 vs vinorelbine/ifosfamine for non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy (PBC). Am Soc Clin Oncol 1776, 1999
12. Kavanagh JJ, Winn R, Steger M, Nelson-Taylor T, Edwards K, Rodgers R, Borst J, Kudelka A, Hu W, Verschraegen CF: Docetaxel for patients with ovarian cancer refractory to paclitaxel, an update. Am Soc Clin Oncol 1423, 1999
13. Valero V, Jones SE, Von Hoff DD, Booser DJ, Mennel RG, Ravdin PM, Holmes FA, Rahman Z, Schottstaedt MW, Erban JK, Esparza-Guerra L, Earhart RH, Hortobagyi GN, Burris HA: A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. J Clin Oncol 16: 3362–3368, 1998

Address for offprints: Elisabeth I. Heath, The Johns Hopkins Oncology Center, 1650 Orleans Street, Room G89, Baltimore, MD 21231, USA; Phone: (410) 955-8974, E-mail: heathel@jhmi.edu