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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 Protocol E1293

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The aim of this study was to evaluate the clinical efficacy and safety of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy. Docetaxel 100 mg m^{-2} was administered as a 1 hour intravenous (IV) infusion every 3 weeks to 41 patients. Patients were premedicated prior to each course with dexamethasone, diphenhydramine and cimetidine. Clinical response and toxicity were determined. Objective responses were seen in seven of 41 eligible patients (two complete responses [CRs] and five partial responses [PRs], for an objective response rate of 17% (90% confidence interval [CI], 8% to 30%). The most common toxicity was grade 4 neutropenia, which occurred in 88% of patients; 46% of patients required a dose reduction following an episode of neutropenic fever requiring antibiotic therapy. Additional patients have had reversible grade 3–4 toxicities including nausea, vomiting, stomatitis, diarrhea, fatigue and peripheral neuropathy. Ten patients have had grade 1–3 hypersensitivity reactions. Alopecia has been seen in the majority of patients. Fluid retention grade 1–3 has been observed in patients. Docetaxel administered on this schedule is an active agent in adenocarcinomas of the upper gastrointestinal tract. Further investigation of this drug should be conducted in multi-drug combination programs.

Keywords: docetaxel; adenocarcinoma of upper gastrointestinal tract.

INTRODUCTION

Adenocarcinoma of the esophagus or stomach, a relatively common disease is highly lethal, with less than 20% of all newly diagnosed patients expected to live for 5 years or more. The use of radical surgery or radiotherapeutic techniques have had little impact on the dismal prognosis of the overwhelming majority of patients. There is no consistently effective single agent or combination chemotherapy for widespread gastric carcinoma. It is therefore necessary to continue

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to screen promising new agents to search for those which have activity against this disease so that effective systemic cytotoxic drug treatments may be designed.

Docetaxel (Taxotere) is a semisynthetic taxane, prepared from a non-cytotoxic precursor extracted from the needles of the European yew tree (*Taxus baccata*). Docetaxel was initially selected for clinical study because it was more potent than paclitaxel in promoting abnormal microtubule stabilization and a more potent antimitotic agent in some tissue culture systems [1–5]. Early work with animal tumor models suggested docetaxel had activity against a broad spectrum of tumor types [6].

Phase I trials of docetaxel began in 1990 and, of the several schedules studied [7-11], the 1 hour infusion repeated every 3 weeks was selected for further evaluation. In this schedule, myelosuppression was the major dose limiting toxic effect; the majority of phase II trials administering docetaxel 100 mg m^{-2} over 1 hour every 3 weeks. Docetaxel has a broad spectrum of anti-tumor activity with response rates greater than 20% observed in non-small cell lung [12–16], breast [17–22], ovarian [23,24], squamous head and neck [25], bladder [26] and gastric cancer [27].

This study which was activated in September, 1993 evaluated the anti-tumor activity of docetaxel in the treatment of patients with adenocarcinoma of the upper gastrointestinal tract (G-E junction, stomach) previously untreated with cytotoxic chemotherapy.

PATIENTS AND METHODS

Eligibility criteria

Patients were required to have measurable, histologically confirmed adenocarcinoma of the upper gastrointestinal tract, with advanced disease not potentially curable by surgery or radiation and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Patients were required to have adequate bone marrow function (WBC $\geq$ 4000 cell ml^{-1} and platelets $\geq$ 100 000 ml), normal liver function (bilirubin $\leq$ 1.5 mg %) and normal renal function (serum creatinine $\leq$ 1.5 mg %). Patients must not have received prior chemotherapy and patients who had prior radiation therapy to areas of measurable disease were ineligible unless progression in these sites had occurred in the interim or unless there was measurable disease outside the area of prior radiation.

Patients were informed of the Phase II investigational nature of the treatment and the toxicities that might be anticipated from such treatment. The study was approved by the institutional review boards of each of the participating centers.

Study parameters

Before therapy, all patients had a complete history and physical examination, complete blood cell count and platelet count, serum biochemical and electrolyte profile, urine analysis, ECG, and chest X-ray. Computed tomographic (CT) scans and X-rays that were used to document indicator lesions for measurable disease were taken within 2 weeks before initiation of treatment. Assessment of anti-tumor responses was made every 12 weeks, if a CT scan was required to document measurable disease, and after every cycle, if physical examination provided adequate assessment of measurable disease. Toxic effects were evaluated according to the Common Toxicity Criteria, which is based on the original ECOG grading system [28].

A complete response (CR) was defined as the complete disappearance of all detectable malignant disease for at least 4 weeks. Partial response (PR) was defined as $\geq$ 50% decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions for at least 4 weeks without an increase in size of any area of known malignant disease or the appearance of new lesions. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% over original measurements in all known malignant disease with no appearance of new areas of malignant involvement over 8 weeks or more. Progression was defined as the occurrence of new lesions or an increase of $\geq$ 25% in the sum of the products of the original biperpendicular measurements.

Drug formulation and preparation

Docetaxel was supplied by the National Cancer Institute (Bethesda, Maryland) as a concentrated sterile solution that contained 80 mg of the drug in 2 ml of polysorbate 80. The drug was diluted with 5% dextrose or 0.9% saline solution to a maximum docetaxel concentration of 1 mg ml^{-1}. The final amount of the drug was administered in 250 ml of solution over 1 hour. Administration was repeated every 21 days until disease progression was documented or until toxic effects precluded further therapy. The starting dose was 100 mg m^{-2}. If grade 1–3 myelosuppression or grade 4 neutropenia occurred with recovery within 21 days, patients were retreated at full dose except in the case where grade 4 neutropenia (absolute neutrophil count $<$ 500 per mm^3) was associated with a temperature $>$ 38°C requiring parenteral antibiotics, or if grade 4 neutropenia was of greater than 7 days duration; then patients were retreated after recovery with a 25% lower dose. Prophylactic therapy with colony-stimulating factors was not used during the initial course but could be used at the investigator's discretion in subsequent

Table 1. Patient characteristics.

No. entered		41
Male/Female		33/8
ECOG PS	0	12
	1	28
	2	1
Age (years)	Median	63
	Range	31–79
No. courses	Median	4
	Range	1–17
Site of primary:	Distal esophagus	1
	G.E. Junction	7
	Stomach	33

courses. Docetaxel was held until resolution of grade 3–4 non-haematologic toxicity to grade 0–1, then reinstituted at 75% of the previous dose. Premedication to prevent hypersensitivity reactions was administered: dexamethasone 20 mg orally 12 and 6 hours prior to docetaxel administration and diphenhydramine 50 mg and cimetidine 300 mg intravenously 30 minutes prior to the docetaxel infusion.

Statistical analysis

The response rate is reported as a percentage of all eligible patients, and the exact confidence limits for response rate follows the method of Atkinson and Brown [29] for multi-stage studies, as this trial was designed to permit early stopping if docetaxel appeared ineffective in this patient population. Progression-free survival and overall survival are calculated according to the method of Kaplan and Meier [30]. The progression-free survival curve drops at the time of progressive disease or death without progression. Both progression-free survival and overall survival are measured from the date of study entry.

Table 2. Major sites of disease

Site	No. Patients
Residual primary	26
Liver metastases	23
Abdominal lymph nodes	20
Extra abdominal lymph nodes	6
Lung mets	3
Pleural-based mets	2

RESULTS

Patient characteristics

Forty-one patients were enrolled from September, 1993 to March, 1995. Their demographic characteristics are included in Table 1. All 41 patients were analysed for toxic effects, and all were assessed for response. In 26 patients (63%), the primary tumor had not been surgically removed. The most common metastatic sites were the liver (23 patients) and abdominal lymph nodes (20 patients) (Table 2).

Toxicity

The dose of docetaxel was reduced at least once in 22 patients (54%). Toxicities are summarized in Table 3. Neutropenia was the principal haematologic and significant adverse event. Thirty-six of the 41 patients had one or more episodes of grade 4 neutropenia. Neutropenia complicated by fever was seen in 19 patients (46%). Although four patients had grade 3–4 anemia and 34 patients had seven grade 1–2 anemia, it was difficult to ascribe anemia unequivocally to the drug.

Table 3. Toxicities incidence in 41 patients

	None 0	Mild 1	Moderate 2	Severe 3	Life threatening 4	Lethal 5
Neutropenia	0	0	1	1	36	0
Anemia	1	11	23	3	1	0
Fever/infection	20	2	14	4	0	1
Nausea	18	15	1	5	0	0
Vomiting	27	6	4	1	1	0
Stomatitis	31	4	1	2	1	0
Diarrhea	26	6	3	2	2	0
Liver	17	17	3	3	1	0
Pulmonary	31	2	4	5	0	0
Hypersensitivity	34	1	1	1	2	0
Fluid retention	31	4	5	1	0	0
Cardiac	37	2	0	1	0	1
Metabolic	25	14	1	0	0	1
Neuro-sensory	25	9	3	1	0	0
Neuro-motor	29	4	1	4	0	0
Fatigue	18	10	7	3	0	0
Alopecia	15	6	17	–	–	–

Values = number of patients.

Table 4. Responses to Taxotere

Response	No. of patients	Sites
CR	2	Pleural-based mass and local recurrence
		Abdominal and extra-abdominal lymph nodes
PR	5	Liver, residual primary
		Abdominal lymph nodes
		Pleural-based mass
		Liver
		Abdominal lymph nodes
Stable	3	Liver, abdominal nodes
		Residual primary
		Liver, abdominal lymph nodes
PD	26	
Unevaluable:	5	
Early death:	4	
Refused treatment after one course:	1	

The most frequently observed non-haematologic side effects were: alopecia, mild to moderate nausea and vomiting, diarrhea, fatigue, stomatitis and peripheral neuropathy and usually managed without the need for dose reduction.

Hypersensitivity reactions, mild to moderate, characterized by flushing, skin rash and sometimes shortness of breath, were observed in five patients. They occurred shortly after the initiation of the first docetaxel infusion; permanent discontinuation of docetaxel owing to these reactions was not necessary in any patient.

Forty-one patients were evaluated for fluid retention. All patients received two doses of dexamethasone prior to every cycle as premedication to prevent hypersensitivity reactions, but this regimen may also have contributed to the prevention of cumulative edema. Because fluid retention is an unusual toxicity, a specific grading scale was utilized for peripheral edema, non-malignant pleural effusion, and non-malignant ascites. Grade 1: asymptomatic; grade 2: peripheral edema: symptomatic and/or requiring diuretics, pleural effusion or ascites: symptomatic, not requiring drainage and grade 3: peripheral edema: symptomatic, resulting in drug discontinuation, pleural effusion or ascites: symptomatic requiring drainage. Fluid retention was observed in 10 patients, but was grade 1–2 in nine of these patients. Sixteen patients received at least six courses of treatment. One of these patients developed grade 3 fluid retention and, although responding to treatment, required discontinuation of treatment.

Four patients experienced lethal toxicities during the first cycle of therapy: (1) sepsis, which was clearly attributable to treatment; (2) metabolic acidosis in a patient who had metastatic disease to the liver and developed liver failure; (3) a cardiac death in a diabetic patient; and (4) a patient who died of unknown cause at home without an autopsy.

Response

Among the 41 eligible patients, seven patients achieved a major response including two complete responses and five partial responses. This is 17% as the point estimate, with exact two-stage confidence limits ranging from 8% to 30%. (Table 4). The two patients who achieved a complete response received 11 and eight courses of docetaxel. The patient who received eight cycles of drug progressed 6 months after study entry; the patient who received 11 cycles of drug was last known in response 19 months after study entry. Four of the five patients who achieved a partial response have progressed, after 3, 8, 8, and 15 months since study entry. One partial responder remains in response 8 months after study entry. The protocol defines stable disease over an 8 week time frame. Two patients achieved stable disease lasting 7 and 12 months from study entry. A third patient achieved stable disease lasting 3 months from study entry, but then withdrew from the study due to a decline in his performance status and began non-protocol chemotherapy. (At that point, the patient was censored for time to progression in our calculations). One patient with stable disease developed a transient ischemic attack after five courses and refused further therapy (it is not known if the transient ischemic attack could be associated with docetaxel, or an underlying disease). Disease progression occurred in 26 patients.

Response could not be assessed in five patients: one refused further docetaxel chemotherapy following the first course, and four patients had early death: one patient with no known previous cardiac history died of unknown cause at home 16 days after initial treatment; one patient 11 days after initial treatment was brought to the emergency room with cardiac arrest and was not successfully resuscitated. This patient had known insulin-dependent diabetes mellitus and had an episode of hypoglycemia a week prior to his death. One patient developed sepsis, dehydration, renal failure and died 21 days after initial treatment and one patient with major metastatic disease to the liver developed metabolic acidosis a day following treatment, followed by hypotension with subsequent liver failure and expired 6 days after initial treatment.

One patient who had a complete response discontinued further treatment after 11 courses in the presence of fatigue and peripheral neuropathy. This patient whose original primary (gastric cardia) had been resected had a local recurrence and a pleural based metastatic mass. Another patient who had a complete response initially had a gastro-esophageal junction primary resected and subsequently developed metastatic disease to abdominal and hilar lymph nodes. This patient had a complete response based on CT scans after four

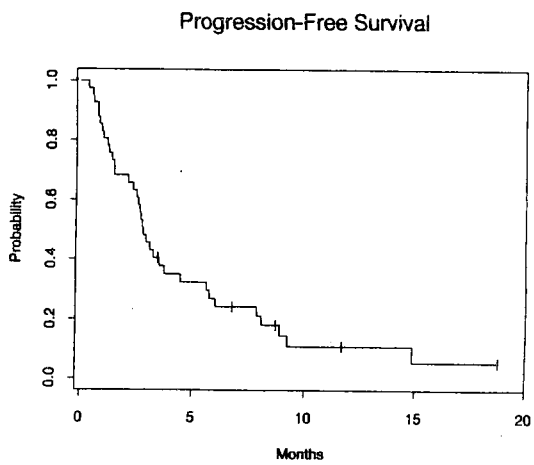

Fig. 1. Kaplan–Meier estimate of progression-free survival.

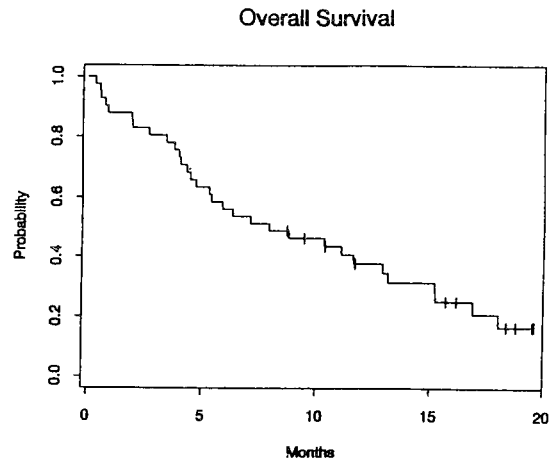

Fig. 2. Kaplan–Meier estimate of overall survival.

courses, was maintained on therapy and subsequently progressed after eight courses.

Five patients had partial responses; responses occurred in a variety of metastatic sites including the liver (two patients), abdominal lymph nodes (two patients) and a pleural based mass (one patient). Three of these patients had their primary resected. Sites of primary disease included pylorus (two patients), cardia (one patient) and gastro-esophageal junction (one patient). One patient discontinued therapy after seven courses while still responding due to neurotoxicity and subsequently progressed. One patient required discontinuation of protocol treatment due to fluid retention after 11 courses, one progressed after 17 courses, one progressed after six courses and one patient is continuing on treatment with a response of liver metastases.

Thirty-four of 41 patients have progressed or died without documented progression. Median progression-free survival was 2.8 months. One patient remains alive and progression-free 18.7 months after study entry. Of the 41 patients, 31 have died. Median overall survival is 7.9 months. Median follow up for the 10 surviving patients is 15.9 months. The Kaplan–Meier estimate of overall survival at 18 months is 17% (Figs 1 and 2).

DISCUSSION

The results of this clinical trial indicate that docetaxel is an active drug against adenocarcinomas of the upper gastrointestinal tract. The results confirm a Phase II study from the European Organization for the Research and Treatment of Cancer (EORTC) Early Clinical Trials Group using the same dose and schedule of docetaxel in which eight out of 33 evaluable patients achieved a partial remission (24%) [27]. The duration of response and toxicities in that study were similar to those observed in this trial. The response rate achieved with docetaxel should be viewed in respect to the single-agent activity and combination regimens observed with the most active conventional drugs in use in this disease. 5-fluorouracil, which has been examined extensively, produces a response rate of approximately 20% [31]. Other drugs with reported activity include mitomycin C, cisplatin, doxorubicin, methotrexate and trimetrexate [32]. Complete responses with single agents are rare, however, and partial responses have been relatively brief.

Various combinations of active drugs have been reported to improve the response rate among patients with advanced gastric carcinoma. A combination of fluorouracil, doxorubicin, and mitomycin C has been associated with a 30–40% response rate and has been the most widely prescribed regimen for patients with advanced disease [33]. Despite an initial high response when a combination of etoposide, doxorubicin, and cisplatin was used by German investigators [34], in subsequent trials, this regimen was considerably less effective and extremely toxic [35,36]. A combination of fluorouracil, doxorubicin, and high-dose methotrexate has also been associated with a significant improvement in response rate [37]. Despite these higher rates of response to chemotherapy, the median survival associated with multidrug therapy has generally ranged from 6 to 10 months, and the overall effect of such treatment, as compared with less toxic, single-drug therapy, on survival remains debatable [38].

Neutropenia was the major toxicity observed and required a dose reduction in nearly half of patients due to associated fevers. The frequency of grade 4 neutropenia after a 1 hour docetaxel infusion is similar to that observed when paclitaxel is given at relatively high doses ($\geq$ 175 mg m^{-2}) over 24 hours. Short infusions of paclitaxel produce much less severe myelosuppression. This observation suggests that the differences in the two drugs in their

intracellular retention and characteristics of microtubule formation noted preclinically may have an impact on schedule-related effects in patients [39].

Significant hypersensitivity reactions observed initially with docetaxel are largely preventable by premedication with dexamethasone, diphenhydramine and cimetidine. This hypersensitivity reaction is one that was observed with paclitaxel and was thought to be due to the vehicle used for formulation in paclitaxel-induced reactions. However, the vehicle used in the formulation for docetaxel is different.

The syndrome of cumulative fluid retention characterized by weight gain, peripheral edema and nonmalignant effusions is unique to docetaxel and the etiology is unknown. Usually several cycles of treatment may be administered before edema becomes evident. In this study, 16 patients received at least six courses of treatment and only one patient required discontinuation of treatment due to grade 3 fluid retention. The use of dexamethasone prior to each treatment may have contributed to the prevention of this toxicity.

It is clear that docetaxel clinically is not simply a semisynthetic paclitaxel. In a Phase II trial of paclitaxel administered as a 24 hour continuous infusion at 250 mg m^{-2} in a similar group of patients, 22 patients were assessable for response and there was only one partial response in a patient with liver metastases [40]. In a Phase II trial of paclitaxel administered as a 24 hour continuous infusion at 250 mg m^{-2} repeated every 21 days in patients with either metastatic or local-regional unresectable carcinoma of the esophagus, 50 patients were evaluated for toxic effects and response [41]. In this study, 32 patients had adenocarcinoma, and 18 had squamous cell carcinoma. Among the 32 patients with adenocarcinoma, 11 (34%) (10 with measurable disease) achieved either a complete (one patient) or a partial response. Among the 18 patients assessed for response with squamous cell carcinoma, five achieved a partial response, with a response rate of 28% (three patients with measurable disease). Further clinical investigations with docetaxel in patients with adenocarcinomas of the upper gastrointestinal tract are warranted based on the experience reported here and the European experience. Studies of docetaxel in combination with other drugs active in this disease should be undertaken.

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