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
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 ≥ 4000 cell ml⁻¹ and platelets ≥ 100 000 ml), normal liver function (bilirubin ≤ 1.5 mg %) and normal renal function (serum creatinine ≤ 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 ≥ 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 ≥ 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 mm³) 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