Phase II trial of taxol in patients with adenocarcinoma of the upper gastrointestinal tract (UGIT)

The Eastern Cooperative Oncology Group (ECOG) Results

Avi I. Einzig1,2, Stuart Lipsitz3, Peter H. Wiernik4 and Al B. Benson III5
1Department of Medicine, Albert Einstein College of Medicine; 2Address for reprints: Avi I. Einzig, M.D. Department of Oncology, Albert Einstein College of Medicine, 1825 Eastchester Road, Bronx, New York 10461; 3ECOG Statistical Center Data Management Office, 303 Boylston Street, Brookline, MA; 4Department of Oncology, Montefiore Medical Center, Bronx, N.Y.; 5Department of Medicine, Division of Hematology/Oncology, Northwestern University of Medical School, Chicago, Illinois, USA

Key words: Taxol (paclitaxel), upper gastrointestinal tumors

Abstract

Taxol was administered as a 24-hour continuous infusion at 250 mg/m² in this Phase II trial in patients with adenocarcinomas of the upper gastrointestinal tract (UGIT). Twenty-five patients were entered between July 1991 and June 1992, twenty-three were eligible and were evaluated for toxicity and twenty-two were assessable for response. There was one partial response (4.5%) in a patient with liver metastases, with a duration of 6 months. Toxicity was primarily neutropenia. Taxol as a single agent appears to have little activity in adenocarcinoma of the UGIT.

Although its incidence in the United States has been decreasing, gastric cancer remains a relatively common disease. It is also highly lethal, with less than 20% of all newly diagnosed patients expected to live for five years or more. The use of radical surgical 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.

Taxol is a novel antimicrotubule agent that enhances tubulin polymerization and microtubule stability. It is a plant product derived by alcoholic extraction from the bark of Taxus brevifolia, the pacific yew. Over the last several years Taxol has been identified as an active agent in several human malignancies including non-small cell lung cancer, refractory ovarian cancer, breast cancer, and malignant melanoma [1–7].

This study which was activated in July, 1991 evaluated the antitumor activity of Taxol 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

To be eligible, 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 ≥ 4,000 cell/uL and platelets ≥ 100,000/uL), 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 antitumor 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 ECOG grading system [8]. 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 a $\geq 50\%$ decrease in the product 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 of 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 areas of original measurements.

Drug formulation and preparation

Taxol was supplied by the National Cancer Institute (Bethesda, Maryland) as a concentrated sterile solution 6 mg/ml in a 5 ml ampule (30 mg/ampule) in polyoxymethylated castor oil (Cremaphor EL) 50% and dehydrated alcohol USP 50%. The drug was diluted in 1000 ml of 0.9% sodium chloride injection, USP or 5% dextrose injection before administration and in-line filtration with a 0.2 mm filter was used with all Taxol infusions.

Taxol was administered as a continuous intravenous (IV) infusion during a 24-hour period for a total dose of 250 mg/m$^2$. The dose was reduced to 200 mg/m$^2$ for grade 3–4 neutropenia, grade 3–4 thrombocytopenia and subsequent courses continued at the reduced dose. Hematopoietic colony-stimulating factors were not recommended in this study. Because of the known toxicity of Taxol and/or the Cremaphor vehicle, precautions before treatment for the possibility of acute hypersensitivity reaction were taken. All patients were premedicated with dexamethasone, diphenhydramine, and cimetidine as previously reported [9]. Any patient who developed severe anaphylaxis despite the precautions was removed from the study. For other grade 3 or 4 toxicity, treatment was held until patients recovered completely or to grade 1 status.

Statistical analysis

This Phase II study of the efficacy of Taxol in adenocarcinoma of the upper gastrointestinal tract was designed to detect a regimen with at least a 20% response rate. Based on the fact that a response was observed in the first 15 patients who were evaluated, the study was extended.

Results

Between July 1991 and June 1992, 25 patients were entered onto this study. Their demographic characteristics are included in Table 1. Twenty-three patients were eligible (two patients were canceled prior to initiation of therapy, one died due to rapidly progressive disease and the other developed an acute elevation of bilirubin due to rapidly progressive disease). These 23 eligible patients were evaluated for toxicity. Twenty-two patients were assessable for response (one patient developed a severe hypersensitivity reaction during the initial course of treatment).