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Results of a Phase II study of weekly docetaxel and carboplatin in Stage IIIB (with effusion) or Stage IV non-small cell lung cancer patients age ≤65 and performance status 2

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Summary This study explores if advanced NSCLC patients with ECOG PS 2 and age ≤65 years can benefit from weekly docetaxel + carboplatin, with acceptable toxicities. Fifty-nine eligible patients with Stage IIIB (effusion) or Stage IV NSCLC were registered. Patients received docetaxel 35 mg/m^2 and carboplatin AUC = 2 on Days 1, 8, and 15 every 28-day cycle (maximum 8 cycles). Endpoints were 1-year survival, tumor response, PFS, and safety. Among the 59 eligible patients, the 1-year survival was 28% and median survival was 6 months (range: 1—24.3). The median duration of response for CR + PR was 5.4 months (range: 2.3—9.7), 1-year progression-free survival was 14% (median of 3.7 months, range < 1—22.8). Patients received a median of 3 cycles (range: 1—9); 14 patients (24%) had toxicity-related reductions. Responses were: 1 CR (2%), 5 PR (10%), 22 SD (45%), and 21 PD (43%). Forty-nine patients were evaluable for response; 10 patients were non-evaluable due to: radiotherapy (1), withdrew consent (3), insurance issues (1), and early toxicity (1 each; dyspnea, weakness, and rash), and other illness (2). Fifty-eight patients were evaluable for safety. The primary Grade 3 or 4 toxicities were neutropenia and fatigue (10% each), nausea (9%), dehydration (7%), and vomiting (5%). A 12% response rate (plus 45% SD) confirms the relatively poor outcome of patients with advanced NSCLC who are PS 2. Toxicities of docetaxel + carboplatin are comparable to other regimens and this combination may provide an alternative for this group of patients. Further studies correlating patient characteristics with response are necessary.

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1. Introduction

The primary goals of therapy for patients with advanced disease are increased survival time, palliation of symptoms, and prolongation of progression-free survival [1—3]. Meta-analyses of trials comparing best supportive care versus chemotherapy have shown a survival benefit from chemotherapy [4—7]. The symptom improvement, weight gain, and improvement in performance status suggest that chemotherapy can be an appropriate palliative therapy for late stage disease.

With currently available treatment, median survival averages 9—10 months in advanced NSCLC in patients with good performance status (0—1); however, those patients with poor performance status (2+) generally survive only 4—6 months [8]. The combination of docetaxel and carboplatin has previously been shown to have efficacy in PS 0—1 patients with NSCLC with acceptable toxicity [9—11]. Our trial was conducted to study the combination of docetaxel and carboplatin in patients $\leq$65 years of age with PS 2, with a focus on 1-year survival and severity of toxicity.

2. Methods

2.1. Study design and treatment

This was a Phase II, open-label trial of weekly docetaxel and carboplatin in patients with histologically or cytologically confirmed Stage IIIB with effusion or Stage IV NSCLC. All patients were treated with the combination of docetaxel (Taxotere®, Aventis Pharmaceuticals Inc., Bridgewater, NJ) 35 mg/m^2 by IV infusion over 30—60 min and carboplatin (Paraplatin®, Bristol—Myers Squibb Company, New York, NY), AUC = 2, infused IV over 15—30 min weekly, on Days 1, 8, and 15, for 3 weeks followed by 1 week of rest. Cycles were repeated every 28 days. Patients were premedicated with oral dexamethasone 4 mg for 3 doses taken orally the night before, the morning of, and the evening after docetaxel administration. Treatment was continued until disease progression or unacceptable toxicity occurred, at which time the patient was taken off treatment.

The protocol was approved by a Central Institutional Review Board, and all patients signed an informed consent form before being enrolled into the study.

2.2. Patients

Between May 25, 2001 and September 15, 2003, a total of 59 patients with advanced NSCLC were enrolled in this study. Patients were $\leq$65 years of age with a PS 2 on the ECOG scale. If major surgery or radiotherapy was conducted prior to this study, patients were fully recovered for at least 3 weeks prior to treatment. Patients were required to have an absolute neutrophil count (ANC) of $\geq$1500 mm^{-3}, platelet count of $\geq$100,000 mm^{-3}, hemoglobin of $\geq$9 g/dL, direct bilirubin of $\leq$1$\times$ the institutional upper limit of normal (ULN), serum creatinine within institutional ULN, transaminases (ALT and/or AST) $\leq$2.5 ULN. Patients had no active serious infection or underlying medical condition and had not received any chemotherapy for their current disease. Pregnant or lactating females were excluded.

2.3. Assessments

Review of inclusion and exclusion criteria, completion of the informed consent, a pregnancy test (when indicated), and a medical history were completed at screening. A physical examination including vital signs, height and weight, assessment of ECOG PS, complete blood count (CBC) with differential and platelet count, physical and radiological tumor assessments, and laboratory tests (total bilirubin, serum creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, serum calcium) were conducted at screening, at scheduled intervals throughout the study, and at the end of therapy. At follow-up, a CBC with differential and platelet count, a survival assessment, and laboratory tests were performed every 3 months. Toxicity was assessed prior to each cycle, at the end of therapy, and for 30 days following the last treatment.

Tumor assessments were performed every other cycle. Assessments of other sites of disease were performed only if a complete response (CR) was claimed.

2.4. Response criteria and toxicity

Patients were evaluable for response if they received $\geq$2 cycles with at least one follow-up tumor assessment using the RECIST criteria [12]. All patients who received at least one dose of study drug were included in the safety analysis. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (Version 2.0).

2.5. Statistical analysis

The primary objective of this study was to determine the 1-year survival rate in patients with Stage IIIB (with effusion) or IV NSCLC. Secondary endpoints were duration of response (DoR), progression-free survival (PFS), survival, and toxicity. Responses were defined as per RECIST criteria [12]. DoR (overall) was measured from the first date that measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrent or progressive disease was objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started), or last date of follow-up for patients who did not progress.

A total of 59 patients were enrolled to detect a 1-year survival rate of 30% using a one-sided alternative with a type I error rate of 5% and a power of 84%. The progression-free survival was defined as the interval from the date of start of treatment to the date of last contact, progression, or death from any cause. The survival time was defined as the interval from the date of start of treatment to the date of last contact or death from any cause. The progression-free and survival were analyzed using the method of Kaplan—Meier [13]. SAS Version 8.0 was used to run the analysis (SAS Institute Inc., Cary, NC).