Bortezomib for Patients with Advanced-Stage Bronchioloalveolar Carcinoma

A California Cancer Consortium Phase II Study (NCI 7003)

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Background: Bronchioloalveolar carcinoma (BAC), a subtype of non-small cell lung cancer, is a difficult disease to treat with low response rates with cytotoxic chemotherapy. Bortezomib, a proteasome inhibitor, has demonstrated objective responses in patients with BAC in early-phase clinical trials. We conducted a phase II study of bortezomib in patients with advanced-stage BAC.

Methods: Patients with advanced BAC, adenocarcinoma with BAC features or BAC with adenocarcinoma features, and less than two prior regimens were eligible. Prior epidermal growth factor receptor (EGFR) inhibitor therapy was allowed. Bortezomib was administered intravenously at 1.6 mg/m^2 on days 1 and 8 of every 21-day cycle until disease progression or unacceptable toxicity. The primary end point was response rate. The Simon two-stage design was used.

Results: Forty-two patients were enrolled, and the study was halted early for slow accrual. Patient characteristics were female 55%, median age 68 years, and Eastern Cooperative Oncology Group performance status of 0 and 1 in 31 and 11 patients, respectively. Twenty-six (62%) patients had received prior therapy with an EGFR inhibitor. A median of four cycles of therapy were administered. Objective responses were noted in 5%, whereas 57% had disease stabilization. The median progression-free survival and overall survival were 5.5 and 13.6 months, respectively. Grade 3 diarrhea and fatigue were noted in three and five patients, respectively.

Conclusions: Bortezomib is tolerated well and is associated with modest anticancer activity in patients with advanced BAC, including patients who progressed on EGFR inhibitor therapy.

Key Words: Bortezomib, Proteasome inhibition, BAC, Bronchioloalveolar carcinoma, NSCLC.

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Bronchioloalveolar carcinoma (BAC) is a subtype of adenocarcinoma of the lung, which is characterized by unique biology and clinical behavior. According to the World Health Organization classification (1999), it is defined as "an adenocarcinoma with a pure bronchioloalveolar growth pattern without evidence of stromal, vascular or pleural invasion."[1] BAC accounts for approximately 3 to 4% of all lung cancers.[2] In addition, 10 to 15% of patients with adenocarcinoma of the lung have BAC features when evaluated under microscopy. In recent years, the incidence of BAC seems to be on the rise.[3] Compared with other subtypes of non-small cell lung cancer (NSCLC), a greater proportion of women and never-smokers present with BAC.[4]

Despite the favorable prognosis for patients with BAC compared with invasive adenocarcinoma, responsiveness to standard cytotoxic chemotherapy has been poor.[5] Two phase II studies of paclitaxel as therapy for advanced BAC reported low response rates and modest survival.[6,7] Recently, the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, has resulted in a somewhat higher response rate and improvement in survival for patients with advanced BAC. In a phase II study by the Southwest Oncology Group, gefitinib was associated with a response rate of 17% and a median survival of 13 months in patients with advanced BAC, better than historical results for chemotherapy alone. Similar results were noted in another

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phase II study with gefitinib for patients with advanced BAC.[8] The response rate in that trial was 13%, and the median survival was 13.2 months. Erlotinib has also demonstrated modest anticancer effects in a phase II study for patients with advanced BAC.[9] In particular, patients with an activating EGFR mutation had a very high response rate of 83% with erlotinib. Cetuximab, a monoclonal antibody against EGFR, was evaluated as monotherapy for BAC in a phase II study by the Eastern Cooperative Oncology Group (ECOG 1504).[10] Despite a low response rate, the median time-to-progression and overall survival (OS) were approximately 4 and 13 months, respectively. Although these studies have demonstrated a role for EGFR inhibitors for the treatment of BAC, the benefit in wild-type tumors is modest at best. There is a clear need to develop other agents for the treatment of this disease, given the poor prognosis for advanced BAC.

Bortezomib is a small molecule proteasome inhibitor that has been approved by the United States Food and Drug Administration for the treatment of refractory multiple myeloma and refractory or relapsed mantle-cell lymphoma. Clinical data suggest that it is active in the treatment of NSCLC with a single-agent response rate of approximately 10%.[11] Bortezomib has also demonstrated similar modest efficacy when given in combination with various chemotherapeutic agents in patients with advanced-stage NSCLC.[11–13] Furthermore, objective responses to bortezomib in patients with BAC have been anecdotally reported in case reports and in the initial phase I trials of this agent.[14–16] On the basis of these observations, we conducted a phase II study to formally evaluate the efficacy of bortezomib in patients with advanced BAC.

Although the approved schedule of bortezomib involves intravenous administration on days 1, 4, 8, and 11 every 3 weeks, we pursued a weekly regimen for this study to minimize patient inconvenience and toxicity. The weekly schedule has been studied by Papandreou et al.[17] and was associated with promising efficacy and good tolerability in patients with advanced prostate cancer. With a dose of 1.6 mg/m^2, the desired biological effects were noted in peripheral blood mononuclear cells and in tumor biopsies. The weekly schedule has also been found to have comparable efficacy and a favorable safety profile in patients with multiple myeloma.[18]

PATIENTS AND METHODS

The primary objective of this phase II study was to determine the objective response rate with bortezomib in patients with advanced BAC. Secondary objectives included determination of OS, progression-free survival (PFS), toxicity, and the safety of bortezomib administered on a weekly schedule.

Inclusion Criteria

Patients with histologically confirmed stage IIIB/IV BAC or adenocarcinoma with BAC features were eligible. Other salient inclusion factors were presence of measurable disease, age older than 18 years, ECOG performance status of 0, 1, or 2, and life expectancy greater than 3 months. Absolute neutrophil count (ANC) $\geq$1500/μl, platelet count $\geq$100,000/μl, total serum bilirubin within institutional normal limits, and serum hepatic transaminases level $\leq$2.5 times institutional upper limit of normal were required for eligibility. For patients with an elevated serum creatinine level, the creatinine clearance had to be $\geq$60 ml/min/1.73 m^2. Patients could have received one prior chemotherapy regimen. Prior treatment with an EGFR inhibitor was allowed. A minimum of 3-week interval from prior chemotherapy and a 2-week interval from prior EGFR inhibitor therapy were required for study initiation. Patients with unstable or untreated brain metastasis, prior therapy with bortezomib, grade 2 or greater neuropathy, serious uncontrolled comorbid illness, and history of another advanced cancer were excluded. Pregnant or lactating women were not included. All patients were required to sign a written informed consent. This open-label, multicenter study included participation from academic institutions in four National Cancer Institute-sponsored phase II consortia and their community partners. The clinical trial protocol was approved by the respective Institutional Review Boards of all participating institutions.

Treatment and Assessment

Bortezomib was administered intravenously over 3 to 5 seconds at a dose of 1.6 mg/m^2 on days 1 and 8 of each 21-day cycle. Treatment was continued until disease progression, development of unacceptable toxicity, or patient decision to withdraw from the study. Patients were required to have an ANC of more than 1500/μl and platelet count of 100,000/μl before initiation of each new cycle of treatment. On day 8, the ANC and platelet counts had to be above 1000/μl and 75,000/μl, in which case the patient was given the same dose of bortezomib as on day 1. If the counts were either 500 to 999/μl or 50,000 to 75,000/μl, respectively, the dose was reduced by 0.3 mg/m^2. If the ANC and/or platelet counts were less than 500/liter and 50,000/liter, day 8 therapy was held, and the patient was reevaluated the following week for drug administration. If the dose of bortezomib was reduced on day 8 for two consecutive cycles, then the day 1 dose was also reduced for all subsequent cycles by 0.3 mg/m^2. The dose of bortezomib was also reduced for grade 1 peripheral neuropathy with pain or grade 2 by 0.3 mg/m^2 and held for grade 3 until resolution to grade 1 or less. Bortezomib was to be discontinued permanently if patient developed grade 4 neuropathy. For all other drug-related grade 3 or 4 toxicities, bortezomib was held until resolution to grade 1 or less and subsequently restarted with a dose reduction. All appropriate supportive care measures were allowed in the event of nonhematological toxicities. A maximum of two dose reductions were allowed per patient.

Study Evaluations

Patients underwent a physical examination, assessment of height, weight, vital signs, and performance status at baseline and at the initiation of each new cycle of therapy. Serum chemistry studies and complete blood count with differential were performed at baseline and before each cycle. Complete blood count with differential count was also evaluated once a week throughout the study. Computed