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Phase II study of the proteasome inhibitor bortezomib (PS-341, Velcade®) in chemotherapy-naïve patients with advanced stage non-small cell lung cancer (NSCLC)☆

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ABSTRACT

The primary objective of this study was to determine the objective response rate of bortezomib as a first-line therapy in patients advanced stage NSCLC. Advanced/metastatic NSCLC patients with measurable disease, adequate organ function, ECOG performance status of 0–2, and no prior chemotherapy for metastatic disease were eligible. Patients received intravenously bolus bortezomib 1.3 mg/m^2/day on days 1, 4, 8 and 11 every 21 days for a maximum of 8 cycles, or until disease progression, or unacceptable toxicity. Tumor response was evaluated after every 2 cycles of therapy. This single-arm phase II study employed the Simon's two-stage design. The study was terminated in the first stage after 14 patients enrolled at 4 institutions. No objective response was observed. Three patients (21%) had stable disease and received 8, 6 and 4 cycles of treatment; the duration of stable disease was 11.5, 4.2 and 3.4 months, respectively. Median time to progression was 1.3 months (95% CI, 0.6–3.0 months); median overall survival (OS) was 9.9 months (95% CI, 2.2–27.0 months). Twelve patients received at least one dose of bortezomib. There were no grade 4 toxicities or treatment related deaths. Grade 3 toxicities included fatigue (N = 1, 8%), deep vein thrombosis (N = 1, 8%) and thrombocytopenia (N = 1, 8%). Although well tolerated, bortezomib monotherapy is not active in this cohort of chemotherapy-naïve, metastatic NSCLC.

1. Introduction

Palliative, systemic chemotherapy remains the cornerstone for the management of patients with metastatic disease or non-operable, locally advanced disease. It reduces cancer-related symptoms and improves quality of life and survival in patients with advanced NSCLC. Thus, it is usually recommended for patients with good performance status [1,2]. Although the first-line treatment of advanced NSCLC has evolved significantly over the past decade, currently doublets of second- and third-generation of chemotherapy regimens seem to reach a plateau with response rate of 30–40%, median survival of 8–9 months and 1-year survival rate of 35–40% [1,2]. There is an urgent need to identify novel targets and treatment strategy to improve the therapy for NSCLC patients. For the elderly patients and patients with poor performance status, single agent chemotherapy regimens are generally used to produce tolerable, modest symptomatic control of disease and improvement in survival. Less toxic and effective therapeutic agents are needed for these patients besides single agent chemotherapy. Recent efforts have been primarily focused on the addition of novel molecularly targeted agents to the foundation of platinum-based two-drug regimens to improve the outcome of first-line therapy for advanced and metastatic NSCLC. The best success so far is the addition of an angiogenesis inhibitor bevacizumab to a platinum-based chemotherapy doublet, which has led to a statistically significant increase in response rate, progression-free survival and overall survival compared to chemotherapy alone (E4599) [3]. Although the improvement in response rate and progression-free survival has been confirmed in a second randomized phase III study of bevacizumab in combination with platinum-based chemotherapy doublets in patients with non-squamous NSCLC (the AVAil study) [4], the overall survival was not statistically significant different between treatment arms [5]. Nevertheless, the median overall survival for patients in all arms of the AVAiL study exceeded 13

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months, which is the longest survival reported in a study of patients with advanced NSCLC, presumably due to the improved post-protocol therapies. Ongoing clinical trials are attempting to build on this success by investigating the clinical efficacy and safety of novel targeted agents, alone and in combination with cytotoxic chemotherapeutic regimens and/or biological agents.

Bortezomib (PS-341, Velcade®, Millennium: The Takeda Oncology Company, Cambridge, MA), a small molecule, modified dipeptidyl boronic acid, is the first selective proteasome inhibitor targeting the ubiquitin-proteasome pathway [6–9]. The ubiquitin-proteasome pathway plays an essential role in the degradation of most short- and long-lived intracellular proteins in eukaryotic cells and has become a valid target for cancer therapy. At the heart of this protein degradative pathway is the 26S proteasome, an adenosine triphosphate-dependent multicatalytic protease, which plays the essential role in proteolytic degradation of damaged, oxidized, or misfolded ubiquitinated proteins. In addition, the 26S proteasome plays a vital role in degrading regulatory proteins that govern the cell cycle, transcription factor activation, apoptosis, and cell trafficking. Bortezomib is a potent, reversible inhibitor of 26S proteasome. It has a broad-spectrum of antitumor effects in many tumor types *in vitro* and *in vivo* by targeting multiple cellular regulatory mechanisms for tumor growth, survival and resistance. Bortezomib directly inhibits 26S proteasome, modulates expression of cyclins and cyclin inhibitors (such as p21, p27), induces G_2/M cell cycle arrest, inhibits degradation of IkB, and modulates apoptosis via Bcl-2, Bax, caspase, TRAIL and death receptor 5 [10–13]. It also potentiates the cytotoxic effect of chemotherapy or radiation [14,15]. It is currently approved in more than 80 countries worldwide. In the U.S., bortezomib is indicated for the treatment of patients with multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

Bortezomib monotherapy has showed promising activity, alone or in combination with chemotherapy, in relapsed or refractory advanced NSCLC patients in phase I and II studies [16–18]. As a second-line monotherapy, bortezomib had a response rate of 8% and stable disease of 21%, median time to progression of 1.5 months and medial survival of 7.4 months [17], which is comparable to that of standard second- and third-line chemotherapy for advanced NSCLC. To the best of our knowledge, there has been no report for its activity in chemotherapy-naïve advanced stage NSCLC patients. This study was designed to evaluate the efficacy and safety of bortezomib in chemotherapy-naïve patients with advanced stage NSCLC.

2. Patients and methods

2.1. Patient eligibility

Patients with histologically or cytologically confirmed NSCLC (squamous, adenocarcinoma, and large cell anaplastic carcinoma) and no prior chemotherapy for stage IIIB with pleural effusion or stage IV disease were eligible. Mixed tumors will be categorized by the predominant cell type unless a small cell anaplastic elements are present, in which case the patient is ineligible. Women of childbearing potential had to have a negative pregnancy test and had to agree to strict contraception while participating in the study. Other key inclusion criteria included: at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) [19], age $\geq$ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate organ and marrow function (leukocytes $\geq$ 3500/μL, absolute neutrophil count $\geq$ 1500/μL, platelet count $\geq$ 100,000/μL, total bilirubin $\leq$ 1.5 mg/dL, and serum creatinine $\leq$ 2.0 mg/dL or creatinine clearance > 20 mL/min).

Exclusion criteria included patients with immune deficiency such as HIV, prior chemotherapy for metastatic disease, patients with uncontrolled, symptomatic brain metastasis, existing grade 2 and more peripheral neuropathy, or history of sensitivity reactions with boron, mannitol, or bortezomib.

The trial (ClinicalTrials.gov Identifier: NCT00200382) was reviewed, approved, and sponsored by Millennium: The Takeda Oncology Company (Cambridge, MA). The local institutional review board at each participating institution approved the protocol. All patients gave written, informed consent.

2.2. Treatment plan

Patients were treated with bortezomib 1.3 mg/m^2/day as a 3–5 s bolus intravenous injection on days 1, 4, 8, and 11 followed by a 10-day rest period every 21 days, which was defined as one cycle. The actual body weight was used to calculate body surface area. At each pretreatment visit, patients underwent a history, physical exam, complete blood count, serum creatinine, electrolytes, liver function tests, and assessment of performance status, and adverse events. Treatment was continued until a maximum of 8 cycles, or disease progression, or severe or intolerable toxicity, or withdrawal of consent. All patients received standard supportive care medications during the study.

2.3. Evaluation of response

All patients underwent computed tomography (CT) of the chest and abdomen and a bone scan within 4 weeks of registration. Tumor response was assessed every 2 cycles by CT using RECIST criteria, and bone scans were repeated if the original bone scan was positive or progressive bony metastatic disease was suspected.

2.4. Evaluation of toxicity and dose modification

Toxicity was graded according to the National Cancer Institute Common Terminology for Adverse Events, version 3.0. Dose limiting toxicity was defined as any grade 4 hematologic toxicity or any grade 2 or 3 neurotoxicity or grade 3 or 4 other non-hematologic toxicity. Treatment interruption was allowed up to 2 weeks until hematologic parameters improved to a hemoglobin $\geq$ 7.5 g/dL, an ANC $\geq$ 750/mm^3, and a platelet count $\geq$ 50,000/mm^3. For patients who experienced grade 3–4 non-hematologic toxicity, bortezomib was held for up to 2 weeks until resolution to grade 0–1, then resumed next cycle with a one dose level reduction. A maximum of two dose reductions was allowed, with the first dose reduction to bortezomib 1.0 mg/m^2/day (i.e., 25%) and the second dose reduction to bortezomib 0.7 mg/m^2/day (i.e., 50%). Neurotoxicity included neuropathic pain and peripheral sensory neuropathy. The occurrence of one grade 2 neurotoxicity required a 25% dose reduction. The occurrence of one grade 3 neurotoxicity or simultaneous occurrence of both a grade 2 neuropathic pain and a grade 1 or 2 peripheral sensory neuropathy required a 50% dose reduction. The occurrence of one grade 4 neurotoxicity or simultaneous occurrence of both a grade 3 neuropathic pain and a grade 3 peripheral sensory neuropathy required permanent discontinuation of bortezomib.

2.5. Statistical considerations

The primary endpoint of the study was objective response rate (complete response plus partial response). This single-arm, open-label, phase II study employed Simon's two-stage Minimax Design [20] to detect an objective response of 20% with 80% power and 5% type I error. This would require at least 4 of 27 evaluable patients to have objective responses. The early stopping rule