Phase II trial of the novel taxane BMS-184476 as second-line in non-small-cell lung cancer

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Background: The purpose of this study was to evaluate the tolerability and efficacy of BMS-184476, an analog of paclitaxel, in patients with advanced non-small-cell lung cancer (NSCLC) progressing or relapsing following at least one prior chemotherapy regimen.

Patients and methods: Fifty-six previously treated advanced NSCLC patients received BMS-184476 at a dose of 60 mg/m² administered intravenously over 1 h every 21 days.

Results: The median number of cycles delivered per patient was five (range one to 17). Dose reduction was required in only 3.8% of cycles. Grade 4 neutropenia occurred in 19.6% of patients, but no grade 4 thrombocytopenia or anemia was reported. Febrile neutropenia was observed in only two (3.6%) patients and there were no life-threatening events. Grade 3/4 peripheral sensory-motor neuropathy was reported in 9% of patients. Other non-hematological toxicities, such as nausea and vomiting, myalgia and arthralgia, diarrhea, and mucositis, were uncommon. Partial responses were observed in eight (14.3%) patients and stable disease in 33 (58.9%). Median progression-free survival was 3.7 months [95% confidence interval (CI) 2.7–5.4] and median overall survival was 10 months (95% CI 6–13.4).

Conclusions: BMS-184476 was well tolerated at the dose of 60 mg/m² and showed evidence of antitumor activity in previously treated NSCLC.

Key words: BMS-184476, novel taxane, NSCLC, second-line chemotherapy

Introduction

Platinum-based chemotherapy remains the standard treatment for patients with advanced non-small-cell lung cancer (NSCLC). It provides symptom palliation and extends survival compared with best supportive care alone [1, 2]. Many advanced NSCLC patients who progress after first-line chemotherapy have an acceptable performance status (PS) and are therefore candidates for additional treatment. However, few chemotherapeutic agents have demonstrated antitumor activity in second-line treatment [3]. In phase II trials, docetaxel demonstrated response rates of 7% to 27% [4, 5], and phase III trials also showed better outcome for patients receiving docetaxel [6, 7], although febrile neutropenia was observed in more than 10% of cases, diminishing the overall benefit.

BMS-184476 is a novel taxane characterized by the replacement of the 7-hydroxyl group found on paclitaxel with a 7-methylthiomethyl ether group [8]. BMS-184476 was designed to combat two mechanisms of paclitaxel resistance: elimination through the P-glycoprotein efflux pump and resistance through tubulin mutations [9]. BMS-184476 was more active than paclitaxel in a P-glycoprotein 170-mediated multidrug-resistant cell line and in the A2780/tax cell line, with encouraging activity in human xenograft tumor models [10]. The 7-methylthiomethyl ether substitution increases the solubility of the drug and reduces the amount of Cremophor EL required as diluent.

Two phase I studies of BMS-184476 as a single agent have been reported. Hidalgo et al. [11] administered doses ranging from 20 to 80 mg/m² every 21 days. Dose-limiting toxicities of neutropenia, febrile neutropenia, diarrhea and mucositis established a maximum-tolerated dose of 60 mg/m². In the second trial [12], BMS-184476 was administered weekly for three consecutive weeks every 28 days, although this regimen was later...
amended to a schedule of days 1 and 8 every 21 days. Neutropenia was the dose-limiting toxicity, and the authors recommended 50 mg/m² on days 1 and 8 every 21 days.

Based on these findings, we designed a phase II study to evaluate the efficacy and toxicity of BMS-184476 at a dose of 60 mg/m² as a 1-h infusion every 21 days in advanced NSCLC patients with recurrent or refractory disease following at least one chemotherapy regimen.

Patients and methods

Eligibility

Eligibility criteria included: histologically confirmed recurrent advanced NSCLC previously treated with at least one chemotherapy regimen (which may have included a taxane); age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1; absolute neutrophil count (ANC) ≥ 1500/ml, platelet count ≥ 100 000/ml, total bilirubin level ≤ 1.5× the upper limit of normal (ULN), and creatinine concentration ≤ 2× ULN. Patients were excluded if they had brain metastases or peripheral neurotoxicity grade ≥ 2 on the National Cancer Institute Common Toxicity Criteria. Bidimensionally measurable disease outside a previous radiotherapy center approved the study.

Informed consent. The institutional ethics committees of each participating institution approved the study. Patients were excluded if they had brain metastases or peripheral neurotoxicity grade ≥ 2 on the National Cancer Institute Common Toxicity Criteria. Bidimensionally measurable disease outside a previous radiotherapy field was required. Before entry into the study, a minimum of 28 days had to have elapsed since previous chemotherapy. Patients who had received prior radiation therapy were considered eligible provided that ≤ 30% of their total bone marrow had been irradiated, but these patients needed to wait 28 days before entering the study. All patients provided written informed consent. The institutional ethics committees of each participating center approved the study.

Pretreatment evaluation

Within 14 days of entry into the study, all patients underwent a complete medical history and physical examination, including a full neurological evaluation, assessment of ECOG PS, a complete blood count and blood chemistry profile. Within 21 days before the initiation of therapy, an electrocardiogram, a chest X-ray and a computed tomography (CT) scan of the chest and upper abdomen were performed. Radionuclide scans of bone and CT scan or magnetic resonance imaging of the brain were performed before the study only if clinically indicated.

Treatment plan

BMS-184476 was administered at a starting dose of 60 mg/m² as a 1-h intravenous infusion every 21 days. All patients received prophylactic premedication with diphenhydramine 50 mg and cimetidine 300 mg given intravenously prior to each BMS-184476 administration. A complete blood count was performed weekly during treatment. Before each subsequent cycle, patients had a clinical history and physical examination, toxicity assessment, complete blood count and biochemical profile assessment.

Treatment was delayed if, on the scheduled day of drug administration, the ANC was <1500/ml or platelet count was <100 000/ml, and was resumed when these minimal levels were reached. Treatment was also delayed for grade 2 or 3 mucositis, dysphagia and/or diarrhea, and was resumed when these toxicities abated. The planned dose was reduced to 50 mg/m² for neutropenic fever, grade 3 or 4 thrombocytopenia, grade 2 neurotoxicity, or any other grade 3 non-hematological toxicity attributable to the previous BMS-184476 dose.

In patients with measurable or evaluable disease, formal assessment of tumor response was repeated after two cycles, and patients showing no evidence of disease progression continued on treatment until withdrawal criteria were met or for a maximum of 12 cycles. Tumor response continued to be assessed every two cycles using World Health Organization (WHO) response criteria. All responses had to be confirmed 28 days or more after the initial assessment.

Statistical analyses

In this patient setting, it was assumed that a true response rate of ≤ 10% was not of clinical interest. A modified Gehan two-stage design was used: 29 response-evaluable patients were to be accrued in the first stage, followed by an additional 16 patients if at least one response was observed in the first stage. This design would result in at least a 95% chance of continuing accrual after the first stage, given a true response rate of at least 10%. With 45 evaluable patients, the exact two-sided 95% confidence interval (CI) would have a maximum width of 25% if the observed response rate is in the expected range of 0% to 20%. Since ~10% of patients were expected to be non-evaluable for response, a total of 50 patients needed to be enrolled.

Progression-free and overall survival were calculated from the first day of treatment to the date of progression or death. Survival curves were constructed using the Kaplan–Meier method. All patients entering the trial were included in the survival analysis.

Results

Patient characteristics

From July 2000 to June 2001, a total of 56 patients from eight participating institutions in Spain were enrolled in this trial. BMS-184476 treatment was withdrawn within the first two cycles in two patients due to toxicity: grade 4 diarrhea and grade 4 neutropenia in one patient, and grade 3 sensory neurotoxicity in a second patient. In addition, a response assessment at cycle 2 was not performed in four patients: one patient died 15 days after starting the first cycle as a result of cardiac failure, two patients had early clinical progression of the disease and one patient went off study due to a pulmonary abscess unrelated to treatment. Therefore, 50 patients received at least two cycles of chemotherapy with tumor reassessment.

Patient characteristics are shown in Table 1. Fifty (89%) patients had received platinum-based and six (11%) had received non-platinum-based chemotherapy combinations. Nine (16%) patients had progressive disease as best response to their prior chemotherapy regimen, and 17 (30%) patients relapsed within 3 months of their last treatment. The median time between the completion of prior chemotherapy and starting BMS-184476 treatment was 123 days (range 15–401).

Toxicity

A total of 330 cycles of BMS-184476 were administered to 56 patients (median five cycles per patient; range one to 17). The median delivered dose-intensity was 19.7 mg/m²/week (98.5% of the planned dose). Dose reductions were required in eight (14%) patients and 33 (12%) cycles were delayed.

Toxicity was assailable in all 56 patients (Tables 2 and 3). Short-lived grade 3/4 granulocytopenia was observed in 49% of patients. Febrile neutropenia requiring hospitalization occurred in two (3.6%) patients. Neither grade 4 anemia nor
grade 4 thrombocytopenia were reported (Table 2). Grade 3/4 peripheral neuropathy was the most common non-hematological toxicity; 4% and 7% of the patients developed grade 3/4 motor and grade 3 sensory peripheral neuropathy, respectively (Table 3). Other non-hematological toxicities, including nausea and vomiting, myalgia and arthralgia, mucositis, and diarrhea, occurred infrequently (Table 3).

Response and survival

Overall response data are summarized in Table 4. Fifty-five patients were evaluable for response; one patient was unevaluable because of an early discontinuation due to a pulmonary abscess unrelated with study therapy. There were eight partial responses, for an overall response rate of 14.6% (95% CI 6.5–26.7). Stable disease was observed in 33 patients and progressive disease in 11, including two patients with early clinical progression. Of the eight responders, three had previously received a non-platinum-based combination and one had received paclitaxel/carboplatin (Table 1). Five of the eight (62.5%) responders had responded to prior chemotherapy. Median duration of response was 7.9 months (95% CI 6.5–11.9). Median progression-free survival was 3.7 months (95% CI 2.7–5.5) (Figure 1). Median overall survival was 10 months (95% CI 6–13.4) (Figure 2), with a 1-year survival rate of 40%.

Discussion

Responses to first-line chemotherapy in advanced NSCLC tend to be partial and short-lived. Median survival is ~8.5 months, with a 1-year survival rate of 35% [1–3]. At the time of disease progression, median survival with best supportive care alone is 4–5 months. In phase II trials, second-line gemcitabine [13] achieved a 19% response rate and 8-month median survival, while with docetaxel, response rates ranged from 16% to 22% and median survival from 7 to 11 months [14]. A phase II study of oral paclitaxel 90 mg/m² in combination with cyclosporine [15] reported a response rate of 23%, time to progression of 3.5 months and median survival of 6 months. The largest phase III randomized trial in second-line
treatment yet reported compared docetaxel 75 mg/m² every 3 weeks with pemetrexed 500 mg/m² every 3 weeks in 571 previously treated NSCLC patients [16]. The median number of cycles given per patient was four in both arms. Response rates (8.8% versus 9.1%), time to progression (2.9 months), median survival (7.9 versus 8.3 months) and 1-year survival (29.7%) were similar in both treatment arms. There was, however, less severe neutropenia, fewer hospitalizations and less need for ancillary measures in the pemetrexed arm.

The present study is the first reported using the novel taxane BMS-184476 in pretreated advanced NSCLC. In tumor models expressing the multidrug (MDR) [8] resistance phenotype BMS-184476 was three to four times more active than paclitaxel and 1.2–1.5 times more active than docetaxel. Phase I studies confirmed its clinical activity as a single-agent in previously treated NSCLC patients [11, 12]. Two phase I studies [17, 18] of BMS-184476 in combination with cisplatin [17] or carboplatin [18] recommended BMS-184476 60 mg/m² followed by cisplatin [17] or carboplatin [18] every 21 days as the dose for further evaluation. Both combinations were well tolerated and showed evidence of antitumor activity in a variety of solid tumors.

In the present phase II study, 56 pretreated NSCLC patients received BMS-184476 at a dose of 60 mg/m² every 21 days, with a 15% response rate, a median progression-free survival of 3.7 months and a median overall survival of 10 months; 60% of patients attained stable disease. Patients received a median of five cycles, almost 90% of the patients received a relative intensity dose of ≥90% and 25% of patients received ≥10 cycles. As with other taxanes, the most significant toxicity was hematological. Grade 3/4 neutropenia was observed in approximately half of the patients. However, the duration was short, which explains the low rate of febrile neutropenia and infections (two patients), in contrast to the 8% to 16% rate of febrile neutropenia observed with docetaxel [4–7]. The most frequent non-hematological toxicity was grade 3/4 peripheral neurotoxicity (9%), mainly sensory. However, 20% of the patients already had grade 1 neuropathy before starting the second-line therapy, probably as a result of prior platinum-based chemotherapy. While 23% of the patients had diarrhea, the frequency of grade 3/4 (7%) events was similar to that described in previous phase I trials [11, 12]. Only five cases of mucositis were observed (9%), three mild and two moderate. Other non-hematological toxicities were infrequent in the present study, and most were of a mild to moderate severity.

In conclusion, BMS-184476 shows a remarkable activity with an excellent toxicity profile when administered at 60 mg/m² in a 1-h infusion every 3 weeks in previously treated advanced NSCLC patients.

References


