ORIGINAL ARTICLE

Phase II Study of a Non-Platinum–Containing Doublet of Paclitaxel and Pemetrexed with Bevacizumab as Initial Therapy for Patients with Advanced Lung Adenocarcinomas

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ABSTRACT

Introduction: Many patients with lung cancers cannot receive platinum-containing regimens owing to comorbid medical conditions. We designed the PPB (paclitaxel, pemetrexed, and bevacizumab) regimen to maintain or improve outcomes while averting the unique toxicities of platinum-based chemotherapies.

Methods: We enrolled patients with untreated, advanced lung adenocarcinomas with measurable disease and no contraindications to bevacizumab. Participants received paclitaxel, 90 mg/m^2, pemetrexed, 500 mg/m^2, and bevacizumab, 10 mg/kg, every 14 days for 6 months and continued to receive pemetrexed and bevacizumab every 14 days until progression or unacceptable toxicity.

Results: Of the 44 patients treated, 50% were women; the median age was 61 years and 89% had a Karnofsky performance status of at least 80%. We genotyped 38 patients with the following results: Kirsten rat sarcoma viral oncogene homolog gene (*KRAS*), 16; anaplastic lymphoma receptor tyrosine kinase gene (*ALK*), three; B-Raf proto-oncogene, serine/threonine kinase gene (*BRAF*) V600E, two; erb-b2 receptor tyrosine kinase 2 gene (*HER2*)/phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene (*PIK3CA*), one; epidermal growth factor receptor gene (*EGFR*) exon 20 insertion, one; and driver 15, none. A total of 23 patients achieved a PR (52%, 95% confidence interval: 37–68), including seven of 16 with *KRAS*-mutant tumors. The overall survival rate at 2 years was 43% with a median of 17 months (95% confidence interval: 10–29). Grade 3/4 treatment-related toxicities included elevated alanine transaminase level (16%), fatigue

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(16%), leukopenia (9%), anemia (7%), elevated aspartate transaminase level (7%), edema (5%), and pleural effusions (5%). Two patients died of respiratory failure without disease progression.

Conclusions: The PPB regimen produced a high response rate in patients with lung adenocarcinomas regardless of mutational status. Survival and toxicities were comparable to those in the phase II reports testing platinum-containing doublets with bevacizumab. These results justify use of the PPB regimen in fit patients in whom three-drug regimens including bevacizumab are appropriate.

Keywords: Lung adenocarcinomas; Bevacizumab; Non-platinum chemotherapy; Pemetrexed; Paclitaxel

Introduction

Cisplatin- or carboplatin-containing doublets with or without bevacizumab are standard initial treatments for patients with advanced lung adenocarcinomas.[1] However, many patients with lung cancers cannot receive cisplatin or carboplatin because of baseline neuropathy, hearing loss, renal insufficiency, heart failure, or other comorbid medical conditions. Because most patients in whom lung cancers are diagnosed are older than 70 years,[2] these toxicities are more likely and more severe.[3] The addition of bevacizumab to a platinum-containing doublet improves response, progression-free survival, and overall survival.[4,5]

Pemetrexed improves survival in patients with adenocarcinomas when administered both initially with cisplatin[6] and as maintenance therapy.[7] As the agent is well tolerated, with the predominant side effects being myelosuppression and fatigue, combination therapy and prolonged administration are possible.[6–8] Bevacizumab has been widely used with pemetrexed and studied in combination with carboplatin or cisplatin as initial therapy that is then continued until progression.[9–12] Progression-free survival significantly improved for patients receiving pemetrexed/carboplatin/bevacizumab followed by pemetrexed/bevacizumab compared with for those receiving paclitaxel/carboplatin/bevacizumab followed by bevacizumab alone.[11] A second trial in which patients were randomized to receive either pemetrexed/bevacizumab or bevacizumab alone after induction with pemetrexed/cisplatin/bevacizumab also demonstrated a significant improvement in progression-free survival in patients continuing both agents after cisplatin therapy was completed.[9,10] Reports of randomized trials of non-platinum containing doublets compared to comparable regimens containing cisplatin or carboplatin as initial therapy for patients with advanced lung cancers are detailed in the Supplementary Table.

Numerous studies have tested regimens without cisplatin or carboplatin, utilizing combinations of gemcitabine, paclitaxel, docetaxel, and vinorelbine.[13–19] In one phase I/II trial evaluating the two-drug combination of pemetrexed with paclitaxel, the response rate was 40%, with a 1-year survival rate of 65% and a grade 3/4 neutropenia rate of 17%.[20] A meta-analysis comparing non-platinum– to platinum-containing doublets[21] found no difference in overall survival and response between the two types of regimens.

To develop a non-platinum–containing regimen using two active agents plus bevacizumab, we conducted this trial of PPB (paclitaxel, pemetrexed, and bevacizumab). The regimen was designed empirically to substitute pemetrexed for carboplatin in the carboplatin/paclitaxel/bevacizumab regimen in use worldwide. Pemetrexed is highly active in lung adenocarcinomas and has bested gemcitabine when each was combined with cisplatin in a head-to-head comparison in persons with lung adenocarcinomas. Previous trials have shown that pemetrexed can be combined with either paclitaxel or bevacizumab. This regimen was designed for use in "fit" patients who are candidates to receive a chemotherapy doublet and bevacizumab. Appropriate patients must have a performance status of 70% or higher; normal kidney, liver and bone marrow function; and no contraindications specific to the drugs that are part of the PPB regimen (allergy, hemoptysis, squamous cell histologic findings, recent stroke or heart attack, or greater than grade 1 peripheral neuropathy).

Materials and Methods

This single-arm, open label, single-institution phase II study was reviewed and approved by the institutional review board. All patients provided written informed consent.

Eligibility

All patients had pathologically confirmed lung adenocarcinomas with stage IV disease at diagnosis or metastatic recurrence after definitive local therapy. Inclusion also required a Karnofsky performance status of at least 70% and measurable disease per the Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST 1.0).[22] Patients had leukocyte counts higher than 4000/mm^3, platelet counts higher than 160,000/mm^3, a bilirubin level less than 1.2 mg/dL, a creatinine clearance of at least 40 mL/min, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels of 37 U/L or lower (or if one level was elevated, no higher than