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Southwestern Oncology Group Phase II Trial (S0526) of Pemetrexed in Bronchioloalveolar Carcinoma Subtypes of Advanced Adenocarcinoma

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Abstract

Bronchioloalveolar carcinoma (BAC) subtypes of lung adenocarcinoma represent approximately 10% to 15% of new non-small-cell lung cancer cases (NSCLC). Based on preclinical data supporting the relevance of alpha-folate receptors in BAC, this trial was designed to assess pemetrexed in patients with this pathologic subtype of lung adenocarcinoma. This trial demonstrated that single-agent pemetrexed is active against this histologic subset.

Background—Pemetrexed, a multitargeted antifolate drug, is an active agent in non-small-cell lung cancer (NSCLC), especially adenocarcinomas. Based on preclinical data supporting the relevance of alpha-folate receptors in adenocarcinoma of the bronchioloalveolar carcinoma (BAC) subtype, this trial was designed to assess pemetrexed in patients with this pathologic subtype of lung adenocarcinoma.

Patients and Methods—Patients with histologically confirmed stage IIIB (with malignant pleural effusion) or stage IV adenocarcinoma with BAC features or pure BAC were eligible. Treatment consisted of pemetrexed, 500 mg/m², administered intravenously every 21 days.

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Results—Of 27 patients enrolled, 24 were eligible and assessable for adverse events: Toxicity was primarily hematologic, consisting of leukopenia/neutropenia, thrombocytopenia, and anemia. The median follow-up among patients still alive (n =8) was 35 months (range, 26–47 months). Among 17 patients with measurable disease, the response rate was 23% (all partial responses; 95% confidence interval [CI], 10%–56%). The median progression-free survival (PFS) and overall survival (OS) were 6 and 25 months, respectively.

Conclusion—Pemetrexed is active and well tolerated and, in patients with adenocarcinoma BAC subtypes, likely related to its underlying mechanism of action as a multitargeted antifolate drug.

Keywords

Lung adenocarcinoma; Bronchioloalveolar carcinoma (BAC); Pemetrexed

Introduction

Lung adenocarcinoma of bronchioloalveolar carcinoma (BAC) subtypes (adenocarcinoma with BAC features and BAC with invasive adenocarcinoma) histologically represent as much as 10% to 15% of new non-small-cell lung cancer (NSCLC) cases and is reported to be more common in female patients, nonsmokers, and younger patients compared with other histologic subtypes of NSCLC.¹ Although recent changes in the pathologic classification of lung adenocarcinoma have redefined the term *BAC*, previous literature and clinical trial data directed against advanced-stage disease, including this study, predate this change and combine invasive adenocarcinoma with BAC features together with pure BAC, which is extensively multifocal throughout both lungs, into a category referred to as advanced-stage BAC. Radiographically, these patients may present with multiple discrete nodules, what appears to be lobar pneumonitis/diffuse infiltrate, or ground glass opacities.² Patients with advanced BAC subtypes are likely to have multifocal disease confined to the lungs and are less likely to have distant metastases. It has been a common belief that advanced BAC is less likely to respond to conventional chemotherapy than are the other histologic subtypes of NSCLC.

The Southwestern Oncology Group (SWOG), a National Cancer Institute (NCI)-funded national cooperative research group, has taken a lead in investigating the efficacy of systemic therapy for advanced BAC. S9714 was the first prospective clinical trial to investigate systemic therapy for this entity, consisting of paclitaxel administered by 96-hour infusion at a dose of 140 mg/m² each 21-day cycle. Of 58 patients with stage IIIB (with malignant pleural effusion) and stage IV BAC enrolled, the response rate was 14%, the median progression-free survival (PFS) was 5 months, and the median overall survival (OS) was 12 months.³ In another phase II SWOG trial (S0126), 136 patients with advanced BAC were treated with gefitinib, 250 to 500 mg daily.⁴ The response rate was 17%, median PFS was 3 to 4 months, and the median OS was 12 to 13 months. Thus the S9714 and S0126 trials provided historical controls for the current study.

Preclinical studies have demonstrated that upregulation of alpha-folate receptors is particularly prominent in NSCLC cell lines characterized as BAC, as well as in

mesothelioma, with enhanced sensitivity to pemetrexed in both these cancers.⁵ Pemetrexed, an active agent in NSCLC, is a multitargeted antifolate drug that inhibits at least 3 of the enzymes involved in folate metabolism (thymidylate synthase [TS], dihydrofolate reductase, and glycylamide ribonucleotide formyltransferase). Of these molecular targets, TS has shown the most promise as a potential predictive biomarker for pemetrexed activity. TS shows differential expression in adenocarcinomas of the lung in general, thus providing an additional rationale for activity of this agent in adenocarcinomas of BAC subtype. Thus based on this preclinical rationale and known clinical efficacy of pemetrexed in NSCLC, SWOG conducted this phase II trial investigating pemetrexed in patients with advanced adenocarcinoma of BAC subtypes (<http://ClinicalTrials.gov> Identifier: NCT00265785).

Patients and Methods

Eligibility

Patients were required to have histologically proven BAC or BAC variants (adenocarcinoma with BAC features, BAC with invasive adenocarcinoma) with stage IIIB (cytologically confirmed malignant pleural effusion) or stage IV disease. Cytologic specimens, such as bronchial brushings, washings, or fine-needle aspiration specimens alone were not acceptable for diagnosis. Patients were required to have a Zubrod performance status (PS) of 0 to 2 and could have either measurable or nonmeasurable disease. Patients with known brain metastases were not eligible. Adequate hepatic function documented by a serum bilirubin level ≤ 1.5 times the institutional upper limit of normal (IULN), renal function with a serum creatinine level ≤ 1.5 times the IULN or a creatinine clearance ≥ 45 mL/min, absolute neutrophil count of $\geq 1500/\mu\text{L}$, and a platelet count $\geq 75,000/\mu\text{L}$ were required. Patients could have had up to 2 previous systemic therapies for BAC.

All patients were informed of the investigational nature of this study and signed a written informed consent in accordance with local institutional review board and federal guidelines.

Treatment

Patients were required to take folic acid, 400 μg , by mouth daily beginning 7 days before the first dose of pemetrexed and continuing until 21 days after discontinuation of pemetrexed. They were also given vitamin B₁₂, 1000 μg , intramuscularly, 7 days before the first dose of pemetrexed and every 3 months while receiving pemetrexed. As an antiemetic, dexamethasone, 4 mg 2 times daily, was given orally the day before, day of, and day after each pemetrexed dose. Pemetrexed, 500 mg/m², was administered intravenously over 10 minutes every 21 days until disease progression, intolerable toxicity, or patient withdrawal from the study.

Assessments

Patients underwent history and physical examination before each treatment cycle every 21 days. Imaging to assess response was performed after every 2 cycles. Baseline computed tomography (CT) and the first 2 follow-up scans were required to be performed with the same CT scanner and technique. Toxicities were graded according to National Cancer

Institute Common Toxicity Criteria, version 3.0. Response assessments were determined based on Response Evaluation Criteria in Solid Tumors (RECIST).

Statistics

The primary goal of this study was to evaluate OS. It was assumed that pemetrexed would not be of further interest in this setting if the median OS was 10 months or less but would be of further interest if the median survival was 15 months or more. With 99 patients accrued over 12 months and an additional 12 months of follow-up, there would be a power of 85% (probability of correctly declaring an agent with a 15-month true median survival to warrant further study) to detect this difference with a significance level (probability of falsely declaring an agent with a 10-month true median survival to warrant further study) of .05. An observed median survival of 13 months or more would be considered evidence that this regimen warranted further investigation. OS and PFS estimates were calculated using the Kaplan-Meier method⁶ and 95% confidence intervals (CIs) for medians were constructed using the Brookmeyer and Crowley method.⁷

The response rate was defined as the number of patients with confirmed or unconfirmed complete or partial responses among the subset of patients with measurable disease (per RECIST) at baseline. Exact binomial CIs were calculated for response outcomes.

Results

The trial was activated on July 1, 2006 and closed on October 1, 2008 (because of slower accrual than anticipated) after 27 patients had been enrolled. Of the 27 patients registered, 1 patient was ineligible because of inadequate renal function. In addition, 2 eligible patients were not analyzable for any of the study endpoints: 1 never received any treatment, and the other initially refused treatment but eventually began treatment 4 months later, which was considered off-protocol treatment and compassionate care. Characteristics of the 24 eligible patients are shown in Table 1. The median patient age was 68 years, with a range of 50 to 83 years. Twelve patients were men and 12 were women. All 24 patients had a PS of 0 to 1. After central pathologic review, 18 patients had adenocarcinoma with BAC features and 6 had pure BAC, all of advanced stage. Ten patients had previously received other chemotherapy and 5 had received an endothelial growth factor receptor tyrosine kinase inhibitor (EGFR TKI).

Grade 4 and selected grade 3 toxicities among the 24 assessable patients are shown in Table 2. The majority of grade 3 and grade 4 adverse events were hematologic. Three patients experienced grade 4 neutropenia, lymphopenia, and/or thrombocytopenia. There were no treatment-related deaths. Seventeen patients had measurable disease according to RECIST at baseline and are included in the analysis of response. There was 1 complete response and 4 partial responses for a response rate of 29% (95% CI, 10%–56%). The median follow-up among patients still alive (n = 8) was 35 months (range, 26–47 months). The estimated median PFS was 6 months (95% CI, 3–14 months) (Figure 1). The estimated median OS was 25 months (95% CI, 15–36 months) (Figure 2).

Discussion

S0526 was initiated in 2006 and focused on lung adenocarcinoma of BAC subtypes, namely, adenocarcinoma with BAC features and pure BAC of advanced stage. Historically, BAC has been defined as lung cancer with lepidic growth of cancer cells along the alveolar wall. In the recent reclassification of lung cancer, the use of the term of *BAC* is no longer recommended by a core of experts from the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society.⁸ Instead, adenocarcinoma with any BAC features are now categorized or classified as (1) adenocarcinoma in situ (AIS), which can be nonmucinous and rarely mucinous; (2) minimally invasive adenocarcinoma (MIA), which can be nonmucinous and rarely mucinous; (3) lepidic predominant adenocarcinoma (nonmucinous); (4) adenocarcinoma, which is predominantly invasive with some nonmucinous lepidic component (includes some resected tumors, formerly classified as mixed subtype and some clinically advanced adenocarcinomas formerly classified as nonmucinous BAC); and (5) invasive mucinous adenocarcinoma (formerly mucinous BAC). Therefore it appears appropriate to state that our trial focused on advanced adenocarcinoma of the lung with any features of lepidic growth under the new scheme of classification of lung cancer.

To our knowledge, SWOG 0526 is the first trial designed to evaluate the efficacy of pemetrexed in patients with BAC subtypes of advanced adenocarcinoma of the lung. Because of slow accrual, our trial was closed after only 27 patients were enrolled over a period of 27 months, whereas 99 patients had initially been planned. This slow accrual was unanticipated in view of our previous SWOG experience with rapid accrual into 2 BAC-specific phase II trials, S9714³ and S0126.⁴ In both these previous trials, eligibility criteria were similar to the current S0526 trial. For the S9714 trial with 96-hour infusion of paclitaxel, 60 patients with advanced BAC were registered over a period of 33 months.³ In the S0126 trial with the EGFR TKI gefitinib, 146 patients were registered over a period of 15 months.⁴ In 2004, Lynch et al first reported the discovery of *EGFR* activating mutations and the association of this molecular abnormality with BAC and sensitivity to EGFR TKIs.⁹ This finding, in combination with approval in the United States of erlotinib, certainly impacted the accrual of patients into the S0526 trial.

Conclusion

Pemetrexed is active and well tolerated in patients with adenocarcinoma BAC subtype. The activity of pemetrexed is likely related to its underlying mechanism of action targeting one of the receptors, the alpha-folate receptor, which is up-regulated in BAC. Despite the smaller number of patients than anticipated, this trial demonstrated that single-agent pemetrexed is active against this subset of adenocarcinoma. Although the response rate and PFS of this trial were comparable to the previous trials specifically designed for treatment of advanced adenocarcinoma of the lung with BAC features (Table 3), the OS of 25 months compares favorably to that of other trials in this setting, with a range of 12 to 17 months. The longer OS seen in S0526 may be due to the use of TKIs after failure with pemetrexed. These data were not captured in this trial.

The tolerability and histologically related efficacy of pemetrexed for adenocarcinoma of the lung has been well demonstrated in previous trials, which have demonstrated that pemetrexed, either as a single agent^{10–12} or in combination with platinum-based agents,¹³ is more efficacious in adenocarcinoma than in squamous carcinoma of the lung. Realizing that *EGFR* mutations are more common in adenocarcinomas, including BAC, *EGFR* TKIs have taken on the primary role in first-line therapy in the subset of patients with tumors harboring activating mutations.¹⁴ Regardless of mutational status, pemetrexed appears to be a reasonable choice for second-line chemotherapy for adenocarcinoma and BAC refractory to TKIs and/or first-line chemotherapy.

There are limitations of the current study. Besides the small number of patients, this study did not capture other characteristics such as *EGFR* mutational status, mucinous vs. nonmucinous features, specific information on previous chemotherapy, and subsequent TKI treatment. These characteristics might have impacted the efficacy of pemetrexed. A future meaningful trial would be to include patients in whom TKIs failed as first-line treatment for *EGFR*-mutated adenocarcinoma and who have not received other chemotherapy.

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Clinical Practice Points

- The adenocarcinoma BAC subtype of the lung is generally resistant to chemotherapy.
- This study demonstrated that pemetrexed possesses moderate activity against this type of lung adenocarcinoma.
- In the future, pemetrexed may be tried as a second-line therapy for BAC which has failed EGFR TKI as a first-line therapy.

Figure 1.
Kaplan-Meier Plot of Progression-Free Survival in 24 Eligible Patients

Figure 2.
Kaplan-Meier Plot of Overall Survival in 24 Eligible Patients

Table 1

Characteristics of 24 Eligible Patients

Number of Patients	24
Male/Female	12/12
Age (y)	
Range	50–83
Median	68
Performance Status	
0	12
1	12
Weight Loss Past 6 Mo	
< 5%	20
> 5%	4
Smoking History	
Current	5
Former	16
Never	3
Histologic Type	
Adenocarcinoma with BAC	18
Pure BAC	6
Previous Chemotherapy	
No	14
Yes	10
Previous EGFR TKI Therapy	
No	19
Yes	5

Abbreviations: BAC = bronchioloalveolar carcinoma; EGFR = endothelial growth factor receptor; TKI = tyrosine kinase inhibitor.

Table 2

Grade 3/4 Toxicities Among 24 Assessable Patients

Toxicities	Number of Patients
Leukopenia/Neutropenia	3
Neutropenic Fever	1
Thrombocytopenia	2
Anemia	2
Lymphopenia	1
Diarrhea	1
Nausea/Emesis	0
Treatment-Related Death	0

Table 3

Comparison of Known Treatment Trials With BAC

Trial	n	RR (%)	PFS, Mo (CI)	OS, Mo (CI)
Paclitaxel (S9714) ³	58	14	5 (3–6)	12 (9–19)
Gefitinib (S0126) ⁴	136	17	3.5 (2.3–3.2)	13 (10.2–17.3)
Erlotinib ¹⁴	101	22	4 (?)	17 (?)
Cetuximab (E1504) ¹⁵	68	7	3 (?)	13 (8–24)
Pemetrexed (S0526) (current study)	24	23	6 (3–14)	25 (15–36)

Abbreviations: OS = overall survival; PFS = progression-free survival; RR = relative risk.