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Results of a Phase II Trial of Carboplatin, Pemetrexed, and Bevacizumab for the Treatment of Never or Former/Light Smoking Patients With Stage IV Non–Small Cell Lung Cancer

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Abstract

We studied first-line treatment of stage IV non–small-cell lung cancer in never or former/light smokers with carboplatin, pemetrexed, and bevacizumab. We found a median progression-free survival of 12.6 months, overall response rate of 47%, and median overall survival of 20.3 months.

Introduction—Bevacizumab- and pemetrexed-based therapies have demonstrated activity in patients with non–small-cell lung cancer (NSCLC) and nonsquamous histologic features. Patients with history of never or light smoking might derive greater benefit from these therapies.

Patients and Methods—The included patients had stage IIIB (malignant pleural effusion) or IV NSCLC with nonsquamous histologic features, adequate organ function, no contraindications to bevacizumab, and no previous cytotoxic therapy. The patients had also never smoked or had smoked ≤ 10 pack years and had quit ≥ 1 year before enrollment. The patients had received 4 cycles of carboplatin (area under the curve, 6), pemetrexed 500 mg/m^2, and bevacizumab 15 mg/kg. Patients without disease progression initiated maintenance therapy with pemetrexed and bevacizumab. A single-arm phase II trial with the primary endpoint of progression-free survival (PFS) was performed. The secondary endpoints were the objective response rate (ORR), overall survival (OS), and toxicity.

Results—From March 2010 to November 2013, 38 eligible patients were enrolled and treated in the trial. The most common histologic type was adenocarcinoma (97%). Most of the patients were women (66%) and never smokers (63%). The median PFS was 12.6 months (95% confidence interval [CI], 8.0–23.9 months). The ORR and OS were 47% (95% CI, 31%–64%) and 20.3

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Disclosure

The authors have stated that they have no conflicts of interest.

months (95% CI, 15.8–30.5 months). The grade 3 or 4 toxicities occurring at rate of ≥ 10% were neutropenia (18%), anemia (16%), fatigue (16%), hypertension (16%), and thrombocytopenia (11%).

Conclusion—The combination of the carboplatin, pemetrexed, and bevacizumab demonstrated activity with acceptable toxicity in patients with a clinical history of never or light smoking.

Keywords

Adenocarcinoma; Bevacizumab; Carboplatin; Light smoker; Never smoker; Pemetrexed

Introduction

Lung cancer is the leading cause of cancer death in both the United States and the world. Tobacco smoking is the dominant risk factor for lung cancer; however, excess focus on this has resulted in inattention to lung cancer deaths not attributable to smoking. If lung cancer in never smokers were considered as a separate disease entity, it would represent the fifth leading cause of cancer death in the United States (after smoking-associated lung cancer, colorectal cancer, breast cancer, pancreatic cancer, and prostate cancer).[1,2]

At the time of trial design in 2008, substantial data were emerging suggesting a differential prognosis and epidemiology of non–small-cell lung cancer (NSCLC) in smoking and nonsmoking patients.[3–7] Even in series in which all patients were treated with chemotherapy without targeted therapy, survival was superior for the nonsmokers.[3,4,8,9] These series have demonstrated that never-smoking patients with lung cancer were younger, more likely to be women, and to have an adenocarcinoma histologic type. Other data had begun to show differential molecular biology between cancers in smokers and nonsmokers and a greater rate of epidermal growth factor receptor (*EGFR*) mutations in patients with a history of light smoking or never smoking.[10,11]

In 2006, the results of the Eastern Cooperative Oncology Group (ECOG) 4599 trial were published, demonstrating an improvement in overall survival (OS) with the addition of bevacizumab to the standard carboplatin plus paclitaxel doublet compared with carbo-platin and paclitaxel in patients with nonsquamous histologic features.[12] Shortly thereafter, in 2008, the results of a trial comparing first-line cisplatin plus gemcitabine and cisplatin plus pemetrexed revealed a histologic type-by-treatment interaction, indicating an improvement in OS with cisplatin and pemetrexed among patients with nonsquamous histologic features.[8] A phase II study of peme-trexed, carboplatin, and bevacizumab followed by maintenance therapy with pemetrexed and bevacizumab revealed promising activity and limited toxicity.[13] We hypothesized that the combination of carboplatin, pemetrexed, and bevacizumab followed by peme-trexed and bevacizumab maintenance would result in superior survival in the clinically defined patient population of never-smokers and former or light smokers. In 2008, when the present trial was designed, routine testing for *EGFR* mutations and anaplastic lymphoma kinase (*ALK*) rearrangements was not standard practice.

Patients and Methods

Eligibility

The included patients were required to have stage IIIB (with malignant pericardial or pleural fluid) or stage IV NSCLC in the American Joint Committee on Cancer staging system, version 6, with nonsquamous histologic features that had not been previously treated with cytotoxic agents. The patients were also required to be a never smoker (defined as not having smoked ≤ 100 cigarettes in the patient's lifetime) or a light smoker (smoked from > 100 cigarettes to ≤ 10 pack-years and had quit smoking ≥1 year before enrollment).[14] The patients were required to be ≥ 18 years old and to have an ECOG performance status of ≤ 1 and adequate organ function. The patients were also required to have no history of coagulopathy and a urine protein/creatinine ratio of ≤ 1.0. Patients with conditions known to impair the safety of bevacizumab were excluded, including active gastrointestinal disease; active cardiac or cerebrovascular arterial disease within 6 months; nonhealing wounds or ulcers; fistulas, perforations, or intra-abdominal abscesses within 6 months; and one-half or more teaspoon active hemoptysis, significant vascular disease, and untreated brain metastases. Finally, the patients with uncontrolled pleural effusions, ascites, or third-space fluid collections were also excluded. After the trial was initiated, the results of the phase III trial of gefitinib compared with carboplatin and paclitaxel became available, and the trial was amended such that patients with a confirmed *EGFR* mutation were required to have received previous therapy with an EGFR tyrosine kinase inhibitor (TKI); patients who had received previous therapy with an EGFR TKI or had an unknown *EGFR* mutation status were eligible.[15]

The present study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the institutional review board of each participating center approved the study. The patients were required to give informed consent before any study-related procedures were performed. This study was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier, NCT01344824).

Treatment

This was a single-arm phase II study of pemetrexed, carboplatin, and bevacizumab followed by maintenance pemetrexed and bevacizumab in patients without progression. Patients received standard premedications with vitamin B_{12}, folic acid, and dexamethasone and standard antiemetics per institutional practice. The patients were given pemetrexed 500 mg/m^2 over 10 minutes, carboplatin area under the curve (AUC) of 6 over 30 minutes, and bevacizumab 15 mg/kg over 90 minutes for the first infusion, 60 minutes for the second infusion, and 30 minutes for subsequent infusions. After 2 cycles, imaging assessments was used to determine the response, according to the Response Evaluation Criteria in Solid Tumors, version 3.0.[16] Subjects without progression were treated for 2 additional cycles followed by disease assessment. Subjects without progression were then treated with maintenance pemetrexed and bevacizumab until progression or unacceptable toxicity. During the maintenance phase, the disease response was assessed every 12 weeks. At progression, it was recommended, but not required, that patients receive erlotinib 150 mg daily as second-line therapy, if they have not previously received erlotinib.

Dose Modifications

Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0, for both dose modifications and toxicity evaluation. Treatment was withheld if the absolute neutrophil count was < 1500/mL or the platelet count was <100,000/mL. The cytotoxic dose reduction to carboplatin AUC5 and pemetrexed 75% was prespecified for the following hematologic toxicities: grade 3 anemia requiring transfusion or grade 4 anemia, grade 4 thrombocytopenia, and grade 4 neutropenia lasting ≥ 7 days. For the first episode of grade 3 febrile neutropenia, growth factor support was initiated. For the second episode of grade 3 febrile neutropenia, any grade 4 neutropenia, or the recurrence of any grade 3 or 4 toxicity after dose reduction, the study therapy was discontinued. The management of neurotoxicity, diarrhea, mucositis, hepatic toxicity, nausea and vomiting, and other nonhematologic toxicities were specified by the protocol.

Statistical Analysis

The primary endpoint of the present study was progression-free survival (PFS), defined as the interval from enrollment to disease progression, as assessed by the investigator, or death. The study sought a median PFS of 10 months for comparison with a historic rate of 6 months. It was estimated that we would need to observe 30 events to achieve 80% power with a 2-sided 0.05 level test in this single-stage, single-arm trial. An intent-to-treat approach was followed in all data summaries. The survival distributions were calculated described using the Kaplan-Meier method.

Results

From March 2010 to November 2013, 38 patients were enrolled and eligible for treatment. The demographic data of the sample are listed in Table 1. Of the 38 patients, 66% were women, and 63% of the patients had never smoked and 37% were former light smokers. The most common histologic type was adenocarcinoma (97%); 1 patient had neuroendocrine carcinoma. Of the 38 patients, 6 (15.8%) had an *EGFR* mutation, 5 (13.2%) had a *KRAS* mutation, and 1 patient had *MET* del14. Of the remaining 26 patients, 22 (57.9%) underwent molecular testing with no driver mutation found, and 4 (10.5%) had inadequate tissue for molecular testing. All 4 of these patients had been previously treated with erlotinib in a Cancer and Leukemia Group B 30,406 clinical trial. Three had a response on the erlotinib-alone arm and the fourth had a response to carboplatin, paclitaxel, and erlotinib.

A single patient had a complete response, and 17 had a partial response, for an objective response rate, as assessed by the investigators, of 47% (95% confidence interval [CI], 31%–64%, Table 2). An additional 40% of patients had stable disease; the disease control rate was 88%. The median PFS was 12.6 months (95% CI, 8.0–23.9 months, Figure 1), and the median OS was 20.3 months (95% CI, 15.8–30.5 months, Figure 2). The response rate for the 24 never-smokers was 54% and was 36% for the 14 former/ light smokers (Table 3). In an exploratory analysis of the 16 patients with any grade of hypertension, the response rate was 56%, with a median PFS of 23.9 months and OS of 43.5 months. In an exploratory analysis of the 6 patients with a confirmed *EGFR* mutation, the response rate was 16.7%, the median PFS was 7.1 months, and the median OS was 31.3 months.

The median number of treatment cycles with carboplatin, pemetrexed, and bevacizumab was 4 (range, 1–4). Of the 38 patients enrolled, 25 initiated maintenance therapy. Of those patients who underwent maintenance therapy, the median number of cycles administered was 11 (range, 1–33). The most common reasons for treatment discontinuation were disease progression (n = 15), treatment-related toxicity (n = 15), study withdrawal (n = 6), and other (n = 2). One patient was still receiving treatment at the last follow-up visit. The treatment-related toxicity is listed in Table 4. The most frequent grade 3 and 4 adverse events were fatigue, anemia, hypertension, and decreased neutrophils.

Of the 38 patients, 24 received second-line therapy. Nine of these patients received erlotinib. Fourteen patients were not treated with second-line therapy, 1 because of an absence of progressive disease and 1 because the response to treatment was sufficient to enable surgery.

Discussion

With a median PFS of > 12 months, the present phase II study met and exceeded its primary endpoint. The median OS of 20 months exceeded both previous phase II[13] and phase III[17] results of the same regimen in patients unselected by smoking status. The results are consistent with the subgroup analysis by smoking status from the phase III PointBreak study comparing carboplatin, paclitaxel, and bevacizumab with bevacizumab maintenance to carboplatin, pemetrexed, and bevacizumab with pemetrexed and bevacizumab maintenance.[17] In the PointBreak study, the OS was similar between the 2 treatment arms in the intent-to-treat patient population (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.96–1.16; $P = .949$). However, in the subgroups of patients with a history of never smoking (n = 108), the patients assigned to pemetrexed-based therapy compared with those assigned to paclitaxel-based therapy experienced a statistically significant longer PFS (HR, 0.48) and a trend toward longer survival (HR, 0.72).[17] The results from the present study have strengthened the hypothesis raised by the PointBreak study that the combination of carboplatin, pemetrexed, and bevacizumab is a particularly effective regimen for patients who have never smoked.

Neither the data from the present study nor from the subgroup analyses on smoking status from existing phase III studies can definitively answer which agent drives any smoking-by-treatment interaction. Two maintenance studies of pemetrexed showed weak trends for greater benefit in never smokers.[18,19] One possible mechanism is mediation by thymidylate synthase levels—the cancer of patients with less smoking history are more likely to be low in thymidylate synthase,[20] and low thymidylate synthase levels have been associated with a response to pemetrexed.[20,21] A meta-analysis of trials adding bevacizumab to platinum-based cytotoxic doublet therapies showed improved PFS and OS, with trends toward superior results in never smokers.[22] We noted in an exploratory analysis superior efficacy in the 16 patients with hypertension as a side effect of treatment, a finding that has previously been reported in association with bevacizumab treatment.[23]

Could these results be explained by specific driver mutations? Studies of the combination of erlotinib and bevacizumab have demonstrated superiority of the combination regimen in patients with *EGFR* mutations.[24,25] Although some retrospective data have suggested

superior efficacy of pemetrexed in patients with the *ALK* gene rearrangement,[26,27] other data have refuted this.[28] Only 6 patients in this study had a confirmed *EGFR* mutation, and all had previously been treated with erlotinib and had developed progression during erlotinib therapy at study entry. The development of routine molecular testing during the course of the present study probably influenced physicians to preferentially enroll patients without a confirmed *EGFR* mutation or *ALK* rearrangement in our chemotherapy-based trial, and patients with an identified oncogenic driver were preferentially enrolled in targeted therapy trials.

Conclusion

Although the cancer of nonsmokers is more likely to have an actionable molecular alteration such as an *EGFR* mutation or *EML4/ALK* gene rearrangement, the relevant targeted therapies control disease for only a finite duration, typically about 1 year. Furthermore, for many nonsmoking patients, mutations have not been defined or are not yet actionable. For both patients with a driver mutation without additional targeted therapies available and those patients without an actionable driver mutation, chemotherapy remains the standard of care. Therefore, defining the optimal regimen for these patients is important. Previous data have shown pemetrexed to be a tolerable and effective agent for patients with nonsquamous histologic features.[29] The results of the present study support existing work that the specific regimen of carboplatin, pemetrexed, and bevacizumab should have significant efficacy for never or former/light smokers. Further study is required to determine the specific molecular mediators of this effect.

Acknowledgments

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Clinical Practice Points

- The combination of carboplatin, pemetrexed, and bevacizumab is a standard first-line treatment of stage IV nonsquamous NSCLC.
- This combination is particularly efficacious in patients with no history of smoking and can be considered a first-line option for such patients when cytotoxic therapy is required.
- All patients with nonsquamous histologic features with stage IV disease, in particular, never smokers should be tested for common driver mutations, such as *EGFR*, *EML4/ALK*, and *ROS1.*

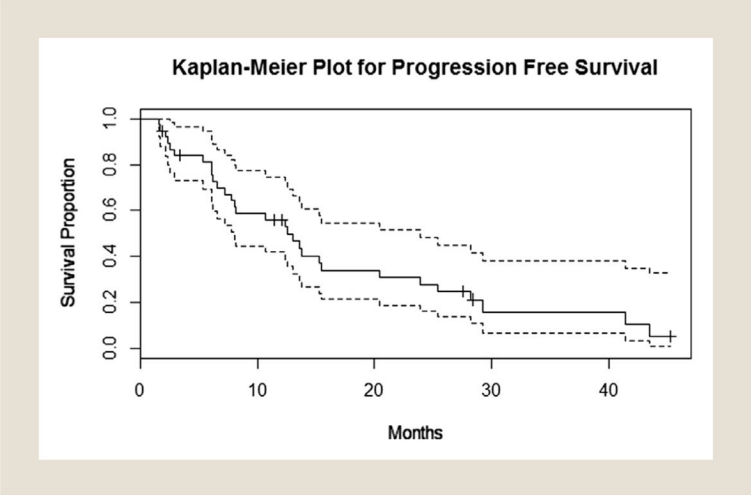

Figure 1.
Progression-Free Survival

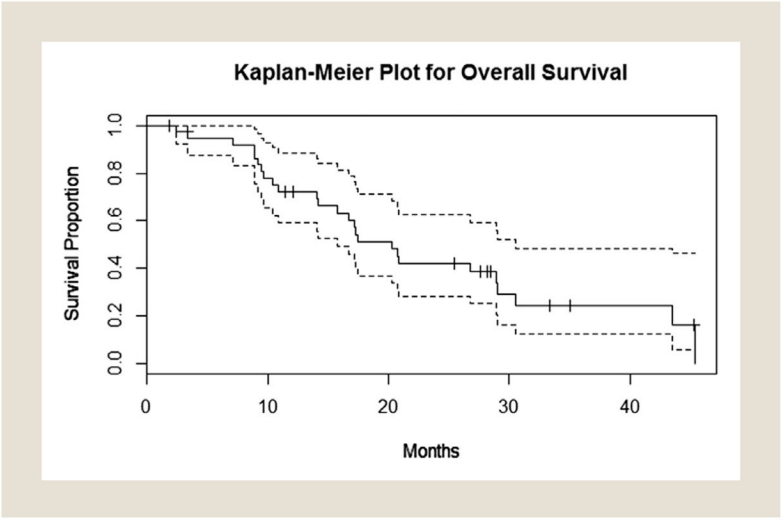

Figure 2.
Overall Survival

Table 1

Patient Demographics

Characteristic	n (%)
Age (year)	
Median	63.5
Range	27–80
Gender	
Female	25 (66)
Male	13 (34)
Race	
White	30 (79)
Black	6 (16)
Asian	1 (3)
Unknown	1 (3)
ECOG PS	
0	18 (47)
1	14 (37)
Not performed	6 (16)
Smoking status	
Never smoker	24 (63)
Former light smoker	14 (37)
Median pack-years	6
Median time since quitting (y)	30
Histologic type	
Adenocarcinoma	37 (97)
Neuroendocrine carcinoma	1 (3)
Previous erlotinib treatment	10 (26)
Mutation status	
EGFR	6 (15.8)
KRAS	5 (13.2)
EML4/ALK	0 (0)
MET del14	1 (2.6)
None (tested and no driver found)	22 (57.9)
Unknown	4 (10.5)

Abbreviations: ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; PS = performance status.

Table 2

Treatment Outcomes

Best Response	Patients (n)
CR	1 (3)
PR	17 (45)
SD	15 (40)
PD	4 (11)
NE	1 (3)
Median PFS (mo)	12.6
Median OS (mo)	20.3

Data in parentheses are percentages.

Abbreviations: CR = complete response; NE = not evaluable; OS =overall survival; PD =progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

Table 3

Outcomes in Select Populations

Characteristic	RR (%)	mPFS (mo)	mOS (mo)
Never smoker (n = 24)	54	13.6	17.5
Former/light smoker (n = 14)	36	12.4	20.8
EGFR mutation (n = 6)	16.7	7.1	31.3
KRAS mutation (n = 5)	80	7.8	17.5
Hypertension as side effect (n = 16)	56	23.9	43.5
Asian race (n = 1)	0	12.4	29.1

Abbreviations: EGFR = epidermal growth factor receptor; mOS = median overall survival; mPFS = median progression-free survival; RR = response rate.

Table 4

Grade 3 and 4 Adverse Events

Toxicity	Patients (n)
Diarrhea	3 (8)
Dyspnea (shortness of breath)	2 (5)
Fatigue (asthenia, lethargy, malaise)	6 (16)
Hemoglobin	6 (16)
Hypertension	6 (16)
Leukocytes (total white blood cell count)	2 (5)
Lymphopenia	4 (11)
Nausea	2 (5)
Neutrophils/granulocytes (ANC/AGC)	7 (18)
Joint pain	2 (5)
Platelets	4 (11)
Vomiting	2 (5)

Data in parentheses are percentages.

Abbreviations: AGC = absolute granulocyte count; ANC = absolute neutrophil count.