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ORIGINAL RESEARCH

Comparative study analyzing survival and safety of bevacizumab/carboplatin/paclitaxel and cisplatin/pemetrexed in chemotherapy-naïve patients with advanced non-squamous bronchogenic carcinoma not harboring EGFR mutation

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Purpose: The majority of Egyptian patients with lung cancer present at a late stage of the disease. Bevacizumab/carboplatin/paclitaxel, as well as cisplatin plus pemetrexed, are both standard regimens for advanced non-squamous bronchogenic cancer. This study compares both regimens, in terms of efficacy and toxicity profile, in Egyptian patients.

Patients and methods: This is a randomized Phase II study comparing toxicity profile and survival in 41 chemotherapy-naïve patients with stage IIIB or IV non-squamous NSCLC, with an ECOG performance status of 0 to 2. The epidermal growth factor receptor (EGFR) mutation detection was performed prior to treatment of all patients. Patients in the first group received: bevacizumab 7.5 mg/m^2 on Day 1 and Day 15; carboplatin area under the curve-5 on Day 1; and paclitaxel 60 mg/m^2 on Day 1, Day 8, and Day 15 every 4 weeks. In the second group, patients received cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 every 3 weeks.

Results: The combination of bevacizumab/carboplatin/paclitaxel demonstrated higher Grade III–IV toxicity than cisplatin/pemetrexed regarding sensory/motor neuropathy ($P = 0.06$), DVT ($P = 0.23$), proteinuria ($P = 0.23$), and hypertension ($P = 0.11$), as well as Grade II alopecia ($P = 0.001$); however, no significant difference in toxicities between both arms was recorded regarding nausea and vomiting ($P = 0.66$), hematological toxicity, febrile neutropenia ($P = 1$) and fatigue ($P = 0.66$). Progression-free survival was similar for both treatment arms with a median of 6 months ($P = 0.978$). Overall median survival was comparable in both arms, 16.07 months versus 16.01 months ($P = 0.89$).

Conclusion: Bevacizumab/carboplatin/paclitaxel and cisplatin/pemetrexed provided meaningful and comparable efficacy in advanced non-squamous bronchogenic carcinoma not harboring EGFR mutation. No significant difference in toxicity was observed between both treatment arms, apart from bevacizumab/carboplatin/paclitaxel-related risks as DVT, hypertension, proteinuria, sensory/motor neuropathy, and alopecia.

Keywords: bevacizumab, non-small cell lung cancer, NSCLC, pemetrexed

Introduction

Primary lung cancers are the most common malignancies after nonmelanocytic skin cancer and the leading cause of human cancer deaths worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancers.[2] In advanced-stage (stage IIIB or IV) NSCLC, doublet combinations of platinum compounds (cisplatin or carboplatin) with gemcitabine, vinorelbine, or taxanes

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(paclitaxel or docetaxel) are reference regimens[3] when compared head-to-head in Phase III studies, these doublets have shown comparable efficacy, with variable differences in toxicity profiles.[4–8]

Pemetrexed is a potent inhibitor of thymidylate synthase[9,10] and other folate-dependent enzymes, including dihydrofolate reductase and glycinamide ribonucleotide formyltransferase.[11] Pemetrexed/cisplatin is currently approved in combination for first-line treatment of malignant pleural mesothelioma[12] and in first-line treatment of non-squamous advanced NSCLC.[13]

Different studies showed more favorable overall survival (OS) for adenocarcinoma related to low thymidine synthetase expression in non-squamous histology.[14,15] Besides this, another study in chemotherapy-naïve patients with squamous and adenocarcinoma of the lung demonstrated that baseline expression of the thymidylate synthetase gene and protein were significantly higher in squamous cell carcinoma compared with adenocarcinoma;[16] however, molecular and other mechanisms that would explain the survival advantage for adenocarcinoma remain unclear. Further molecular-marker studies will help in better stratification of patients to different active regimens.

The addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor to paclitaxel and carboplatin, led to significant survival benefit. However, this efficacy benefit was seen with an increased risk of treatment-related morbidity and deaths.[17]

The recombinant, humanized monoclonal antibody bevacizumab in combination with paclitaxel and carboplatin is approved by the US Food and Drug Administration for first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC.[17–20] Bevacizumab binds to a vascular endothelial growth factor, which is an essential endothelial cell mitogen, a survival factor, and a key factor in tumor-associated angiogenesis.

These two combinations bevacizumab/carboplatin/paclitaxel and cisplatin/pemetrexed achieved better and almost similar OS in different trials, and are standard regimen for advanced non-squamous NSCLC.

The primary aim of the present study is to analyze a toxicity profile as well as the efficacy of both regimens in term of progression-free survival (PFS), with OS as the secondary endpoint.

Patients and methods

During the period from September 2008 to May 2010, 65 chemotherapy-naïve patients presented to Dar Al Fouad Hospital with advanced non-squamous bronchogenic cancer. Sixteen patients were excluded, being epidermal growth factor receptor (EGFR)-mutant. Five patients were excluded because of the presence of brain metastasis. Three others were excluded as well because of an initial presentation with hemoptysis. The remaining 41 patients fulfilled the selection criteria and were assigned to this randomized study.

All patients were eligible if: they had histologically or cytologically confirmed NSCLC, classified as stage IIIB not amenable to curative treatment or stage IV, with at least one unidimensionally measurable lesion, according to the Response Evaluation Criteria in Solid Tumors (RECIST);[21] an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2;[22] and were at least 18 years of age. EGFR mutation detection was performed in all non-squamous NSCLC prior to study entry, using an EGFR mutation detection kit (EntroGen Inc, Tarzana, CA, USA). Patients had adequate bone marrow reserve and organ function, including calculated creatinine clearance ≥45 mL/minutes, based on the standard Cockcroft–Gault formula.[23]

Exclusion criteria included: peripheral neuropathy ≥ Grade 1, according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0; progressive brain metastases; or uncontrolled third-space fluid retention before study entry. Patients were also excluded on the basis on: harboring the sensitizing mutation to the EGFR gene; a recent history of bleeding or thrombotic events and ongoing therapeutic anticoagulation; uncontrolled hypertension; unable to interrupt aspirin and other nonsteroidal anti-inflammatory drugs; or if they were unable or unwilling to take folic acid, vitamin B12, or corticosteroids.

Non-squamous EGFR wild types fulfilling the selection criteria were randomly allocated into the treatment groups on a ratio of 1:1, using a computer system with a closed envelope to one of these two treatment arms:

- Bevacizumab, 7.5 mg/kg — Day 1, Day 15
- Carboplatin, AUC-5 — Day 1
- Paclitaxel, 60 mg/m^2 — Day 1, 8, and 15

➢ or

- Cisplatin, 75 mg/m^2 — Day 1
- Pemetrexed, 500 mg/m^2 — Day 1.

Baseline and treatment assessments

Prior to treatment, all patients underwent a medical history and physical examination, and tumor measurements were taken both for palpable lesions as well as lesions assessed by imaging techniques. Positron emission tomography and ultrasound scans were not permitted. The baseline

assessment method was repeated every other cycle and then every 8 weeks after treatment discontinuation until disease progression. Disease status was assessed in solid tumors according to RECIST.[21]

Twenty patients were assigned to arm 1 (bevacizumab/carboplatin/paclitaxel), and 21 patients were assigned to arm 2 (cisplatin/pemetrexed). The primary endpoints of the study were PFS and toxicity profile and secondary endpoint was OS.

Statistical analysis

Comparison of toxicity was done using Fisher's exact test. Survival was estimated using Kaplan–Meier and log rank for comparing curves. *P*-value is always two tailed; and significance was at the 0.05 level.

Results

In the period from September 2008 to May 2010, a total of 41 patients were randomly assigned (20 patients to bevacizumab/carboplatin/paclitaxel and 21 patients to cisplatin/pemetrexed). The baseline patient and disease characteristics are shown in Table 1.

Efficacy

In terms of response rate, partial response was witnessed in (12/20 patients) in arm 1 and (10/21 patients) in arm 2, while stable disease was seen in (6/20 patients) in arm 1 and (9/21 patients) in arm 2 ($P = 0.81$).

Figure 1 shows the progression-free survival estimate (95% confidence interval), which was similar for both treatment arms with a median for arm 1 of 6 months (5 to 7 months) versus (vs) 6 months (4 to 8 months) for arm 2 as well ($P = 0.978$).

Overall survival estimate (95% confidence interval) for the patient randomly assigned to (bevacizumab/carboplatin/paclitaxel) was almost similar to that of (cisplatin/pemetrexed), 16.01 (11.47–20.55) months vs 16.07 (14.66–17.49) months ($P = 0.89$).

Figure 2 shows the Kaplan–Meier curve for overall survival. Survival at 12 months and 24 months was 80% and 20% for bevacizumab/carboplatin/paclitaxel, respectively, and 85.7% and 33% for cisplatin/premetrexed.

In subgroup analysis to which stage IIIB (nine of 41 patients) was compared to stage IV (32 of 41 patients), the overall survival was 13.99 months vs 16.07 months (Figure 3),

Table 1 Baseline characteristics for randomly assigned patients

	Bevacizumab/ carboplatin/paclitaxel		Cisplatin/ pemetrexed		*P*-value
	%	Number of patients	%	Number of patients	
Age (years)		39–69		31–67	0.68
Mean		53.35		51.62	
<65	85%	(17/20)	85.7%	(18/21)	
≥65	15%	(3/20)	14.3%	(3/21)	
Sex					
Female	25%	(5/20)	28.6%	(6/21)	0.79
Male	75%	(15/20)	71.4%	(15/21)	
Smoking status					
Never smoker	15%	(3/20)	9.5%	(2/21)	0.66
Former/current smoker	85%	(17/20)	90.5%	(19/21)	
Stage of disease					
IIIB	25%	(5/20)	19%	(4/21)	0.72
IV	75%	(15/20)	81%	(17/21)	
Most common metastatic sites					
Stage IV: whole group	75%	(15/20)	80.9%	(17/21)	ND
Bone	86.6%	(13/15)	88.2%	(15/17)	
Liver	66.6%	(10/15)	58.8%	(10/17)	
Suprarenal	40%	(6/15)	41.1%	(7/17)	
ECOG performance status					
0–1	80%	(16/20)	66.7%	(14/21)	0.34
2	20%	(4/20)	33.3%	(7/21)	
Histologic type					
Adenocarcinoma	75%	(15/20)	76.2%	(16/21)	0.79
Adenosquamous	20%	(4/20)	14.3%	(3/21)	
BAC	5%	(1/20)	9.5%	(2/21)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ND, intention not to compare but to describe; BAC, broncho-alveolar carcinoma.

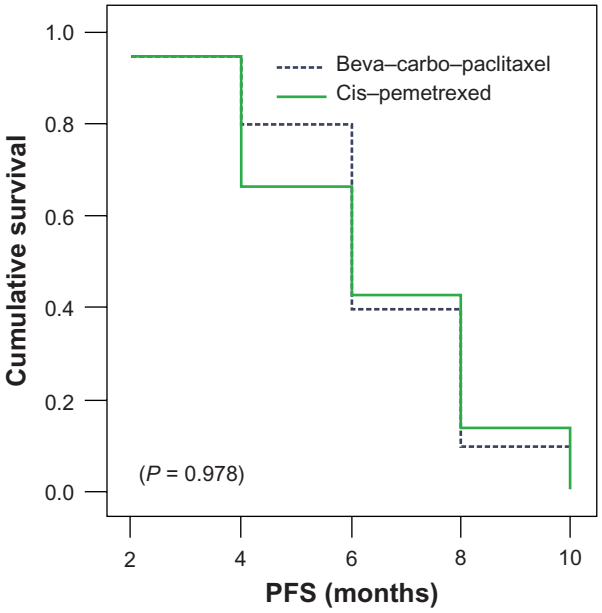

Figure 1 PFS for both treatment arms.
Abbreviations: Beva–carbo–paclitaxel, bevacizumab/carboplatin/paclitaxel; cis–pemetrexed, cisplatin/pemetrexed; PFS, progression-free survival.

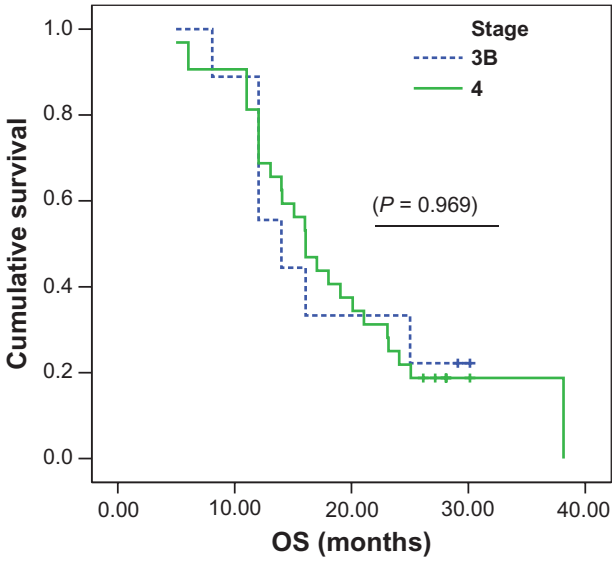

Figure 3 OS according to stage in the whole study population.
Abbreviation: OS, overall survival.

which didn't reach a statistical significance ($P = 0.9697$). However, subgroup analysis to which ECOG 0 to1 (30 of 41 patients) was compared to EGOG II (eleven of 41 patients) showed that the patient with better performance 0 to 1 (Figure 4) tended to achieve better survival at 16.07 months vs 12.05 months ($P = 0.4046$). Finally, subgroup analysis to which positive smoking status (36 of 41 patients) was compared to never-smoker status (five of 41 patients) revealed an overall survival of 16.07 months vs 12.05 months, not reaching statistical significance ($P = 0.6571$).

Safety

According to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0, the grade III–IV drug-related toxicity incidents recorded were neutropenia, anemia, and thrombocytopenia. There was no difference between both arms (neutropenia: 3 of 20 patients in arm 1 vs 4 of 21

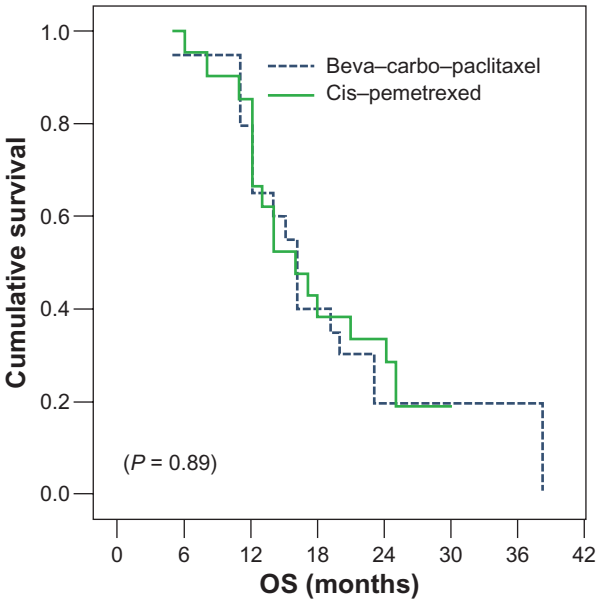

Figure 2 Overall survival for both treatment arms.
Abbreviations: Beva–carbo–paclitaxel, bevacizumab/carboplatin/paclitaxel; cis–pemetrexed, cisplatin/pemetrexed; OS, overall survival.

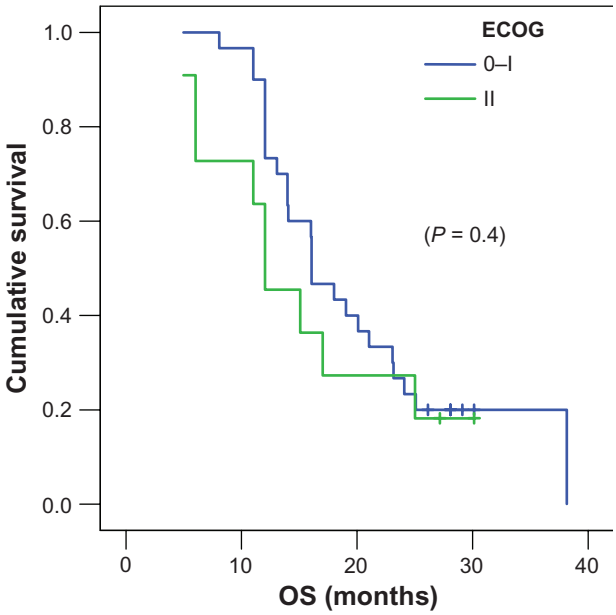

Figure 4 OS by ECOG in the whole study population.
Abbreviations: OS, overall survival, ECOG, Eastern Cooperative Oncology Group.

patients in arm 2 [$P = 1$], anemia: 2 of 20 patients in arm 1 vs 3 of 21 patients in arm 2 [$P = 1$]; and thrombocytopenia: 1 in 20 patients in arm 1 vs 4 of 21 patients in arm 2 [$P = 0.43$]). Febrile neutropenia requiring hospital admission was noted in 1 in 20 patients in arm 1 and 2 in 21 patients in arm 2 ($P = 1$). Nausea and vomiting was in 2 of 20 patients in arm 1 and higher in arm 2 (4 in 21 patients) ($P = 0.66$). Fatigue was noted in 3 in 20 patients in arm 1 and 2 in 21 patients in arm 2 ($P = 0.66$).

Hypertension was also higher in arm 1 (3 of 20 patients) vs no hypertension recorded in arm 2 ($P = 0.11$). Proteinuria also was recorded in arm 1 (2 of 20 patients) and was not recorded in arm 2 ($P = 0.23$). Deep venous thrombosis (DVT) was higher in the bevacizumab-containing arm (4 in 20 patients) but not significantly different compared to arm 2 (2 of 21 patients) ($P = 0.41$). Sensory/motor neuropathy was more evident in arm 1 (8 of 20 patients) vs arm 2 (3 of 21 patients), although not reaching significance ($P = 0.06$). Alopecia (Grade II alopecia) was significantly higher in arm 1 (18 of 20 patients) vs arm 2 (1 of 21 patients) ($P = 0.001$). The toxicity profile difference between both arms is demonstrated in Table 2.

Discussion

It has been reported that the addition of bevacizumab to carboplatin/paclitaxel in previously untreated patients with advanced non-squamous NSCLC was associated with improved OS.[17] On the other hand, the combination of cisplatin/pemetrexed improved OS, when compared to the doublet combination of platinum compound with gemcitabine.[13] Both of these two combinations achieved better and almost similar OS in different trials, and are standard regimen for advanced non-squamous NSCLC. However, direct comparison of efficacy across different randomized clinical studies could lead to some biased conclusions due to different patient populations.

Table 2 Randomly assigned treated patients common toxicity criteria (Worst Grade 3–Grade 4)

Toxicity G3–4 (CTCAE)	Bevacizumab/ carboplatin/ paclitaxel	Cisplatin/ pemetrexed	*P*-value
Hematologic			
Neutropenia	(3/20 patients)	(4/21 patients)	1.0
Anemia	(2/20 patients)	(3/21 patients)	1.0
Thrombocytopenia	(1/20 patients)	(4/21 patients)	0.43
Febrile neutropenia	(1/20 patients)	(2/21 patients)	1.0
Nausea and vomiting	(2/20 patients)	(4/21 patients)	0.66
Fatigue	(3/20 patients)	(2/21 patients)	0.66
Alopecia grade 2	(18/20 patients)	(1/21 patients)	0.001
Hypertension	(3/20 patients)	(0/21 patients)	0.11
Proteinuria	(2/20 patients)	(0/21 patients)	0.23
DVT	(4/20 patients)	(2/21 patients)	0.41
Sensory/motor neuropathy	(8/20 patients)	(3/21 patients)	0.06

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events version 3.0; DVT, deep venous thrombosis.

The issue of bevacizumab dosing in advanced non-squamous NSCLC, whether 7.5 mg/kg or 15 mg/kg, remains discussable and depends on the chemotherapy backbone. In the AVAstin in Lung (AVAiL) study,[24] 15 mg/kg every 3 weeks with paclitaxel/carboplatin in (ECOG 4599) and 7.5 mg/kg every 3 weeks with gemcitabine/cisplatin were studied; yet, in our study, we assumed that 7.5 mg/kg every 2 weeks would be a compromise between toxicity and efficacy, which is probably why we didn't record any life-threatening hemorrhagic side effects or treatment-related mortality.

This study compared both regimens in terms of toxicity and efficacy (response rates, PFS, and OS rates) in a small sample of the Egyptian population. A partial response was observed in 60% in arm 1 and 47.6% in arm 2, while stable disease was seen in 30% in arm 1 and 42% in arm 2. This response rate was meaningful and denoted the comparable activity of both regimens in non-squamous EGFR nonmutant bronchogenic cancer.

The median time to progression in both arms was 6 months, which was also comparable to that achieved in ECOG of 6.2 months and that of the study conducted by Scagliotti et al of 5.3 months.[13]

The combination of bevacizumab/carboplatin/paclitaxel demonstrated higher Grade 3–4 toxicity than cisplatin/pemetrexed, in terms of the well-known bevacizumab/carboplatin/paclitaxel-related hazards, such as sensory/motor neuropathy, DVT, proteinuria, and hypertension, as well as alopecia Grade 2. However, no significant difference in toxicity was observed regarding nausea and vomiting, hematological toxicity, and febrile neutropenia between both arms.

The median survival for both arms was equivalent at 16.07 months and 16.01 months; this is longer than both the median previously reported in ECOG 4599[17] of 12.3 months and the 12.6 months reported in the study conducted by Scagliotti et al.[13] Despite the small size of our study, this better overall survival can be attributed to eventual population-related biological factors. The achieved median survival in both arms reflects the positive effect of both regimens on survival.

Surprisingly, stage IV patients (32 of 41 patients) and smokers (36 of 41 patients) tended to have a better OS than stage IIIB patients (9 of 41 patients) and nonsmokers (5 of

41 patients), which might be attributed to the smaller number of stage IIIB patients and nonsmokers in comparison to Stage IV patients and smokers.

In conclusion, cisplatin/pemetrexed and bevacizumab/carboplatin/paclitaxel provided meaningful and comparable efficacy in advanced non-squamous EGFR nonmutant bronchogenic carcinoma. There was no significant difference in toxicities, apart from in DVT, hypertension, sensory/motor neuropathy, proteinuria, and alopecia, which were more common in the bevacizumab-containing regimen. Their efficacy may allow these to become the preferred regimens, although with special attention to bevacizumab-related risks in certain patients.

These results warrant future prospective studies, specifically designed to evaluate biological markers which may guide the selection of patients most likely to benefit from either of these two regimens.

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Disclosure

The authors report no conflicts of interest in this work.

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