Research Article

Bevacizumab with paclitaxel and carboplatin for locally advanced (Stage IIIB) metastatic adenocarcinoma of lung: A feasibility study from tertiary care center

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ABSTRACT

Background: Lung cancer is the most common cancer and leading cause cancer-related death in worldwide and also in India. Around 42% of these patients have adenocarcinoma. Most of these patients presented in locally advanced stage or metastatic disease. There is no significant difference in effectiveness among different chemotherapy regimens with median survival of 8 months only. Hence, additional treatment option including newer monoclonal antibodies is needed to improve tumor control and survival. Vascular endothelial growth factor (VEGF) is critical determinant of tumor angiogenesis, a process that is necessary component of tumor growth, invasion, and metastasis. Bevacizumab (Bev), a humanized monoclonal antibody (IgG1) targeting VEGF, effective in colorectal cancer, renal cell carcinoma, glioblastoma multiforme, and non-small cell lung cancer and approved for clinical use since 2004. **Objectives:** The aim of our study is feasibility of the combination of Bev with paclitaxel and carboplatin in locally advanced (Stage IIIB) metastatic adenocarcinoma of lung in our institute, N.R.S. Medical College and Hospital, Kolkata. **Materials and Methods:** Between February 2015 and December 2018, ninety-eight previously untreated patients with locally advanced metastatic (Stages IIIB and IV) adenocarcinoma of lung treated with Bev with paclitaxel and carboplatin. Paclitaxel at a dose of 175 mg/m^2, carboplatin at an AUC 6 mg/ml/min, and Bev at a dose of 15 mg/kg given on the 1st day of chemotherapy. Chemotherapy administered every 3 weeks up to 6 cycles with maintenance Bev until disease progression or unacceptable toxicity whichever is earlier. Patients ECOG 2 or more, brain metastasis, squamous cell histology, and hemoptysis were not included in the study. **Results:** The Median overall survival (OS), progression free survival (PFS) were 9.4 and 5.2 months, respectively. Anemia (19%) and neutropenia (16 %) are most common toxicity. **Conclusion:** Bev with paclitaxel and carboplatin in selected patients with adenocarcinoma of lung is safe and confers survival benefit with acceptable toxicity.

KEY WORDS: Bevacizumab; Paclitaxel; Carboplatin; Adenocarcinoma; Toxicity

INTRODUCTION

Lung cancer is the most common cancer and leading cause cancer-related death in worldwide and also in India. Around 42% of these patients have adenocarcinoma.[1] Most of these patients presented in locally advanced stage or metastatic disease.[1] There is no significant difference in effectiveness among different chemotherapy regimens with median survival of 8 months only.[2] Hence, additional treatment option including newer chemotherapeutics is needed to improve survival. Vascular endothelial growth factor (VEGF) is critical determinant of tumor angiogenesis, a process that is necessary component of tumor growth, invasion, and metastasis.[3-5] Bevacizumab (Bev), a humanized monoclonal antibody (IgG1) targeting VEGF, effective

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in colorectal cancer, renal cell carcinoma, glioblastoma multiforme, and non-small cell lung cancer (NSCLC) and approved for clinical use since 2004.[6] Addition of bevacizumab to conventional chemotherapeutics (paclitaxel and carboplatin, gemcitabine and cisplatin, or pemetrexed and carboplatin) resulted in significant improvement in median survival median progression-free survival (PFS).[7] Another rational for the addition of Bev to paclitaxel plus carboplatin is that it improves drug delivery to the tumor.[8] As previously stated that VEGF is key proangiogenic factor, continued inhibition of VEGF is essential to prevent tumor neovascularization or revascularization, which is required for further tumor growth. Hence, after completion of 6-cycle combination regimen (chemotherapy plus Bev), Bev is administered as a single-agent maintenance therapy until disease progression or development toxicity.[9] However, this associated clinically significant bleeding and other toxicity, i.e., modest benefit, toxicity can be significant.[6,7] In one Phase III trial by compared the efficacy and safety of pemetrexed + carboplatin followed by pemetrexed with paclitaxel + carboplatin + Bev followed by Bev in patients with advanced non-squamous NSCLC pemetrexed + carboplatin regimen did not produce significantly better PFS compared with paclitaxel + carboplatin + bevacizumab regimen. Pemetrexed + carboplatin regimen was not superior in PFS, overall survival (OS), and objective response rate (ORR), compared with paclitaxel + carboplatin + Bev regimen. Both regimens were well tolerated, although, toxicity profiles differed.[10] In one systematic review and meta-analysis of randomized controlled trials comparing the efficacy of chemotherapy (CT) plus Bev versus CT alone in previously untreated locally advanced or metastatic NSCLC showed that the combination of CT plus Bev increased the response rate and PFS of patients with NSCLC. With respect to OS, the benefits of Bev remain uncertain.[11] Although Bev approved for clinical use since 2004 by the US FDA and Bev supplied in our hospital for the treatment of patients free of cost by state government, we have limited clinical knowledge regarding safety and feasibility of its clinical use in recommended dose. After getting formal permission from our ethical committee, we wanted to study, whether this combination chemotherapy regimen in recommended dose can be delivered safely in our hospital or not.

MATERIALS AND METHODS

Treatment protocol is depicted in Figure 1. All patients underwent biopsy (bronchoscopic or true cut biopsy), contrast-enhanced CT (CECT) brain, chest abdomen, and pelvis, whole-body 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) CT scan bone scan, and magnetic resonance imaging brain in indicated cases. Between February 2015 and December 2018, ninety-eight previously untreated patients with locally advanced metastatic (Stages IIIB and IV) histologically confirmed adenocarcinoma of lung in our hospital (N.R.S. Medical College and Hospital, Kolkata), treated with Bev with paclitaxel and carboplatin. Paclitaxel at a dose of 175 mg/m^2, carboplatin at an AUC 6 mg/ml/min, and Bev at a dose of 15 mg/kg given on the 1st day of chemotherapy in standard rate of infusion. Routinely, we use pegfilgrastim (6 mg) on day 2 in every patient for neutropenia prophylaxis. Chemotherapy administered every 3 weeks up to 6 cycles with maintenance Bev until disease progression or unacceptable toxicity whichever is earlier. Complete blood count (CBC) on day 8 and day 15 and CBC, liver function tests, kidney function tests, and urine analysis for proteinuria before each chemotherapy routinely performed. CECT brain, chest abdomen, and pelvis or whole-body FDG-PET CT scan performed after the 3rd and 6th cycles to assess response. Patients with ECOG PS score 0 or 1, adequate hematologic, and renal and hepatic function were included in the study. Patients ECOG 2 or more, brain

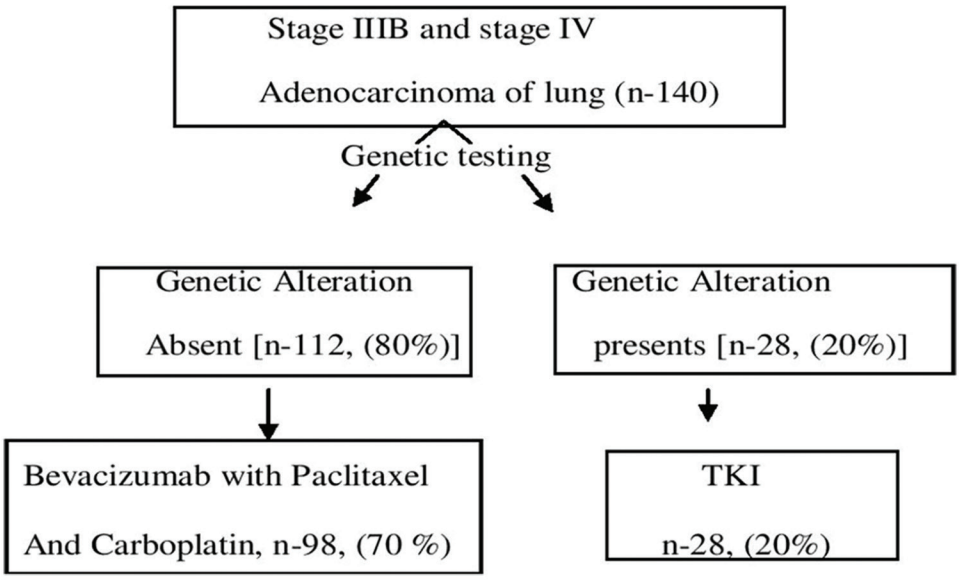

Figure 1: Treatment protocol

metastasis, squamous cell histology, hemoptysis, major surgery within 28 days, using anticoagulant, and uncontrolled hypertension were not included in the study.

RESULTS

Baseline characteristics of treated patients are depicted in Table 1. Median number of chemotherapy cycle is 5 (range 3–9 cycles). Complete response seen in 4% of patients and ORR seen in 62% patients. The median OS is 9.2 months. The PFS is 5.2 months. Rates of adverse events are depicted in Table 2. Hematological toxicity includes neutropenia (16%), thrombocytopenia (10%), and anemia (19%). Non-hematologic toxicity includes hypertension (9%) and bleeding events seen in 6% of patients and peripheral neuropathy seen in 9% of patients. All toxicities were managed safely in our set up without resulting in treatment-related death.

DISCUSSION

In our study the median OS 9.2 months and the PFS 5.2 months. Complete response seen in 4% of patients and ORR was 62%. Anemia (19%) and neutropenia (16%) are most common toxicity. The toxicity profiles in our study were comparable to what has been observed other bevacizumab containing trials.[12]

The median OS reported by different authors ranges from 8.8 months to 13.4 months and median PFS ranges from 6.2 to 6.7 months. In a landmark Phase III trial, the addition of Bev to paclitaxel plus carboplatin in selected patients with NSCLC has significant survival benefit (10.3 months vs. 12.3 months) with increased risk of treatment-related death. with increased risk of treatment-related death.[7] In another phase III randomized trial combining Bev with gemcitabine and cisplatin significantly improved PFS, ORR and offers clinical benefit for Bev eligible patients with advanced NSCLC.[13] In our study, OS and PFS after addition of Bev to platinum-based chemotherapy were comparable to other trials reported in literature [Table 3] with acceptable and comparable toxicities.[6,7,12-14] The incidence of fatal pulmonary haemorrhage and neutropenia less common in our study than what reported in published literature, this may be partly explained by the fact that we have excluded patients with previous history hemoptysis of any amount, central cavitary, necrotic lesion, and squamous cell histology because these conditions are associated with higher incidence of fatal haemorrhage. Less incidence of neutropenia is due to prophylactic use of pegfilgrastim routinely. Headache proteinuria and hypertension observed in the study they manageable with conservative therapy.

The results of our study augment the growing body of evidence that Bev with paclitaxel and carboplatin combination provides important clinical benefit with locally advanced metastatic (Stages IIIB and IV) adenocarcinoma of lung. However, in our study, small number patients are major limitations. Another limitation is our single-arm and non-randomized study.

Table 1: Patient's baseline characteristic

Characteristics	Number of patients *n*=98 (%)
ECOG PS score	
0	38 (39)
1	60 (61)
Age >60 years	72 (73)
Sex	
Male	68 (69)
Female	30 (31)
Stage	
III B	43 (44)
IV	55 (56)
Prior radiotherapy	
Yes	15 (15)
No	83 (85)

Table 2: Adverse events

Adverse events (all grades)	Total *n*=98 (%)
Anemia	19 (19)
Thrombocytopenia	10 (10)
Neutropenia	16 (16)
Hypertension	9 (9)
Proteinuria	5 (5)
Bleeding events	6 (6)

Table 3: OS and PFS in selected contemporary series after the addition of bevacizumab to platinum duplet

Series	OS	Median PFS (month)
Reck *et al*.[12]	Not reported	6.7
Patel *et al*.[13]	13.4 months	5.6
Sandler *et al*.[7]	12.3 months	6.2
Present study	9.4 months	5.2

PFS: Progression-free survival, OS: Overall survival

CONCLUSION

Selected patients with locally advanced metastatic (Stages IIIB and IV) adenocarcinoma of lung and good performance status can tolerate well combination chemotherapy regimen of Bev, paclitaxel, and carboplatin and can be administered safely in our set up and this regimen resulted in improved in OS and PFS.

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