Paclitaxel-Carboplatin versus bevacizumab
Paclitaxel-Carboplatin for treatment of Non-Small-Cell Lung Cancer

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ABSTRACT

Background: Lung cancer is considered as the leading cause attributed to cancer related deaths and approximately 85% of lung cancer patients have non-small-cell lung cancer (NSCLC) and Vascular endothelial growth factor (VEGF) is used to play the major role in regulation of angiogenesis in malignancies.

Aim: The aim of this study was to compare chemotherapy alone in comparison with addition of anti-vegf (bevacizumab) to chemotherapy and assessment of response rate, progression free survival, overall survival in patients diagnosed with non-squamous non small cell lung cancer in Saudi German hospitals in the period between March 2013 and February 2016.

Patients and methods: This study was held between March 2013 and February 2016 in Saudi German hospitals when we performed a randomized study in which 40 patients with recurrent or advanced non-small-cell lung cancer (stage IIIB or IV) received paclitaxel and carboplatin (paclitaxel-carboplatin arm) (20 patients) paclitaxel and carboplatin in addition to bevacizumab (paclitaxel-carboplatin-bevacizumab arm) (20 patients).

Results: The median overall survival was 15.5 months in the paclitaxel-carboplatin-bevacizumab arm as compared with 10.5 months in the paclitaxel-carboplatin arm (P=0.002) and the median progression-free survival was also significantly improved in the paclitaxel-carboplatin-bevacizumab arm reaching (8.4 months versus 5.9 in the paclitaxel-carboplatin arm) for a hazard ratio for disease progression of 0.67 (95% CI, 0.57 to 0.77; P<0.001) and the addition of bevacizumab to paclitaxel and carboplatin improved the response rate as (25 %) in the paclitaxel-carboplatin arm had a response versus (65%) in the paclitaxel-carboplatin-bevacizumab arm (P<0.001) and the rates of hypertension, bleeding, thrombocytopenia, neutropenia, febrile neutropenia, proteinuria were significantly higher in the paclitaxel-carboplatin-bevacizumab arm than in the paclitaxel-carboplatin arm. (P<0.05).

Conclusion: The addition of bevacizumab to the chemotherapy added a significant value to the patients with non squamous NSCLC in terms of response rate, progression free survival and overall survival however with significant side effects.

Key words: Lung cancer; Bevacizumab; Vascular endothelial growth factor
Introduction

Lung cancer is considered as the leading cause attributed to cancer related deaths and approximately 85% of lung cancer patients have non-small-cell lung cancer and there is global rise of lung cancer incidence with overall 5 years survival less than 15% .(1) Tumorogenesis is considered as a multistep process that depends on transformation from normal bronchial epitheliunm to overt lung cancer then continued accumulation of the genetic abnormalities influences the cancer invasion and development of metastases and resistance to the cancer treatment and that can take place throughout chromosomal instability mechanisms.(2) Several aetiological factors have been accused in NSCLC including cigarette smoking , exposure to radon , asbestos and genetic susceptibility.(3) NSCLC has 3 major histological subtypes, adenocarcinoma, large cell carcinoma and squamous cell carcinoma.(4) In early stages stage I and II, and selected cases of stage III, surgery is the corner stone of management followed by adjuvant chemotherapy but in late stages, the unresectable stage III the treatment is chemoradiation and in stage IV the treatment is double agent chemotherapy with or without biological target therapy .(5) After their growth within the bronchial wall and or the lung parenchyma primary lung malignant tumors invade the regional hilar and mediastinal lymph nodes through lymphatics then through the blood vessels to distant organs such as brain, liver and bone.(6) Biopsy can be performed through several methods including CT guided biopsy or bronchosopic biopsy and even through thoracotomy and Positron Emission Tomography (PET scan) is a corner stone in staging and further assessment during treatment and follow up.(7)

Angiogenesis is a landmark for cancer in which there is an angiogenic switch from perturbation in the balance that normally exists between inducers and inhibitors which are produced by both tumor and host cells that lead to a high micro vessels density with overexpression of VEGF which is associated with poor outcome in NSCLC.(8) Vascular endothelial growth factor (VEGF) is used to play the major rule in regulation of angiogenesis in malignancies Increased VEGF expression in non-small-cell lung cancers is associated with increased risks of local recurrences, metastases, and deaths.(9) Preclinical studies have shown that a monoclonal antibody against VEGF ( bevacizumab-avastin) can inhibit the growth of human malignant tumor cells (10).new target therapy agents are needed to overcome the intrinsic or acquired resistance limiting the efficacy of the common anti-tumoral agents (11).

This study was held in Saudi German hospitals and is a randomized study including patients with advanced non-small-cell lung cancer with no prior chemotherapy administration compared to paclitaxel and carboplatin protocol versus paclitaxel and carboplatin plus bevacizumab protocol with bevacizumab dose 15 mg /kg of body weight intravenously every 3 weeks.(12)

Patients and methods

This study was held between March 2013 and February 2016 in Saudi German hospitals as we performed a randomized study in which 40 patients with recurrent or advanced non-small-cell lung cancer (stage IIIB patient -pleural effusion- or IV) received paclitaxel and carboplatin (paclitaxel-carboplatin arm) (20 patients) or paclitaxel and carboplatin in addition to bevacizumab (paclitaxel-carboplatin-bevacizumab arm) (20 patients). Inclusion criteria were patients with an ECOG performance status of 0-2, and adequate hemotologic, hepatic, and renal function and to be histopathologically proved newly diagnosed stage IIIB ( pleural effusion) or stage IV non-squamous NSCLC or recurrent NSCLC with no prior chemotherapy.

Exclusion criteria were histologic evidence of squamous-cell cancer or central nervous system (CNS) metastases, pregnancy or lactation, significant cardiovascular disease and uncontrolled hypertension.

The primary end point was overall survival. In our study patients were randomly assigned to receive paclitaxel at a dose of 175 mg/m2 and carboplatin at a dose of area under the curve (AUC) 6 administered intravenously on day 1 (arm 1), or paclitaxel at a dose of 175 mg/m2 and carboplatin at a dose of area under the curve (AUC) 6 administered in addition to bevacizumab at a dose of 15 mg /kg given intravenously on day 1 and chemotherapy was repeated every 21 days for a total of six cycles unless there was disease progression or marked intolerable toxicity. Patients in the paclitaxel-carboplatin-bevacizumab group continued to receive bevacizumab alone every 3 weeks unless there was disease progression or marked intolerable toxicity.

Afterwards the baseline evaluation assessment took place every 9 weeks by PET scan assessment. Survival was measured as the period from randomization to death , and progression-free survival as the period from randomization to disease progression or death. Event-time distributions were estimated by the Kaplan-Meier method and estimated P values were two-sided and CIs were at the 95% level.

The two groups were well balanced regarding baseline characteristics and the median number of cycles of therapy was five in the paclitaxel-carboplatin arm and seven in the paclitaxel-carboplatin-bevacizumab arm.

The median overall survival was 15.5 months in the paclitaxel-carboplatin-bevacizumab arm as compared with 10.5 months in the paclitaxel-carboplatin arm ( P=0.002). Survival rates were 55% in the paclitaxel-carboplatin-bevacizumab arm as compared with 45% in the paclitaxel-carboplatin arm at 1 year and 27% as compared with 17% respectively at 2 years.

The median progression-free survival was also significantly improved in the paclitaxel-carboplatin-bevacizumab arm reaching ( 8.4 months versus 5.9 in the paclitaxel-carboplatin arm) for a hazard ratio for disease progression of 0.67 (95% CI, 0.57 to 0.77; P<0.001).

The addition of bevacizumab to paclitaxel and carboplatin improved the response rate as (25 %) in the paclitaxel-carboplatin arm had a response versus (65%) in the paclitaxel-carboplatin-bevacizumab arm (P<0.001). (Table 1)
The rates of hypertension, bleeding, thrombocytopenia, neutropenia, febrile neutropenia, proteinuria were significantly higher in the paclitaxel-carboplatin-bevacizumab arm than in the paclitaxel-carboplatin arm (P<0.05).

There were 9 deaths related to toxic effects of the treatment. Two deaths (from gastrointestinal hemorrhage and febrile neutropenia) occurred in patients in the paclitaxel-carboplatin arm and 7 occurred in the paclitaxel-carboplatin-bevacizumab arm; the difference between the groups was significant (P=0.001)(Table 1). Of the 7 deaths in the paclitaxel-carboplatin-bevacizumab group, 4 were due to pulmonary hemorrhage, and 3 due to febrile neutropenia.

Table 1:

<table>
<thead>
<tr>
<th></th>
<th><strong>PACLITAXEL-CARBOPlatin ARM</strong></th>
<th><strong>PACLITAXEL-CARBOPlatin BEVACIZUMAB ARM</strong></th>
<th><strong>P-VALUE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall survival</strong></td>
<td>10.5 M</td>
<td>15.5 M</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>PROGRESSION FREE SURVIVAL</strong></td>
<td>5.9 M</td>
<td>8.4 M</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>RESPONSE RATE</strong></td>
<td>25%</td>
<td>65%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>DEATHS</strong></td>
<td>2</td>
<td>7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 1: Mediastinal mass
Figure 2 (above): Mediastinal mass

Figure 3: (below) Mediastinal mass
Figure 4: Left lung malignant mass (NSCLC)

Figure 5: Left lung malignant mass (NSCLC)
Discussion

In our study the addition of bevacizumab to chemotherapy regimen improved overall survival, progression-free survival and response rate in patients with advanced NSCLC.

Villett et al. stated that bevacizumab increases delivery of the drug to the tumor and the marvelous significant improvement in the response rate in this study and in previous randomized controlled studies of chemotherapy with addition of bevacizumab supports the data that bevacizumab improves overall survival, progression-free survival and response rate in patients with advanced NSCLC.(13)

Jubb AM et al stated in their study the use of bevacizumab in combination with platinum based chemotherapy in treatment of metastatic lung cancer stage IV patients resulted in improvement of response rate and progression free survival which is matching with the results revealed in our study.(14)

Among the 9 other deaths considered to be related to treatment in our study, 5 were due to haemorrhage either pulmonary or gastrointestinal and 4 were due to complications of febrile neutropenia and although neutropenia has not been associated with bevacizumab, however 3 patients in the paclitaxel-carboplatin-bevacizumab group had grade 5 febrile neutropenia. Other studies had as that reported by Giantonio BJ et al and by Jubb AM et al revealed increased rates of neutropenia when bevacizumab was combined with chemotherapy.(14, 15)

The hypertension, and proteinuria in our study are due to bevacizumab. They were manageable and did not need a permanent stop of bevacizumab. This is matched with other literature as reported by Jubb AM et al and Kozloff M. et al in the study of treatment effects and side effects of bevacizumab (15,16).

Conclusion

The addition of bevacizumab to the chemotherapy added a significant value to the patients with non squamous NSCLC in terms of response rate, progression free survival and overall survival however with significant side effects.

References

2. The hallmarks of cancer. Cell 2008;100:57-70


