

Platinum-based Doublet Chemotherapy plus Bevacizumab Without Bevacizumab Maintenance in Advanced Non-small Cell Lung Cancer (NSCLC)

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Abstract. *Background: We report on a retrospective, consecutive non-randomized group of patients who received bevacizumab plus chemotherapy without bevacizumab maintenance. Patients and Methods: Patients with adenocarcinoma subtype of NSCLC and advanced disease received carboplatin and vinorelbine together with bevacizumab for four cycles without bevacizumab maintenance. Overall survival (OS), progression-free survival (PFS), response rate (RR) and toxicity were reviewed. Results: A total of 30 consecutive patients were included in a period of two years. RR, bleeding, thromboembolic and haematological complications were comparable to those of the literature. Median OS and PFS were 8.8 and 4.5 months for patients with performance status (PS) 0-1, while they were 2.6 and 1.2 months for those with PS 2, p-values being 0.006 and 0.039, respectively. Conclusion: The effect of maintenance bevacizumab on OS has not yet been established but it has been proven as being favourable on PFS. Our data suggest that patients with PS 2 should not receive this treatment.*

Non-small cell lung cancer is among the most common types of cancer. The incidence of lung cancer in Denmark is 78/100.000 in men and 68/100.000 in women (2012) (1). The prognosis is generally poor. Standard treatment for advanced NSCLC without epidermal growth factor receptor (EGFR) mutations is platinum-based doublet chemotherapy with the addition of bevacizumab in selected patients.

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Bevacizumab is a humanized monoclonal antibody that inhibits angiogenesis through inhibition of vascular endothelial growth factor-A (VEGF-A). Two large randomized phase III studies [E4599 (2) and AVAiL (3)] investigated the addition of bevacizumab to standard doublet platinum-based chemotherapy, both using bevacizumab maintenance after 4-6 courses of induction treatment. The E4599 trial revealed an increase in median overall survival (OS) from 10.3 months in the group receiving standard treatment with paclitaxel/carboplatin against 12.3 months in the group assigned to same standard chemotherapy plus bevacizumab, for patients with non-squamous histological types ($p=0.003$) and 14.2 months for the adenocarcinoma subtype hazard ratio [HR=0.69]. Progression-free survival (PFS) was 4.5 versus 6.2 months for non-squamous subtypes ($p<0.001$) and 5 versus 6.6 months for adenocarcinoma [HR=0.65], respectively (4). The E4599 trial did not indicate p -values for adenocarcinoma subtypes. The AVAiL trial compared cisplatin/gemcitabine alone and together with bevacizumab at 7.5 mg/kg or bevacizumab at 15 mg/kg and with bevacizumab maintenance. PFS increased from 6.1 in the control to 6.7 months with addition of bevacizumab at 7.5 mg/kg and 6.5 months with bevacizumab at 15 mg/kg ($p=0.0003$ and $p=0.0456$, respectively). These results led to approval of bevacizumab in combination with platinum-based doublet chemotherapy for advanced non-squamous NSCLC, followed by bevacizumab maintenance until progression. Bevacizumab is currently the only anti-angiogenic drug approved for treatment of non-squamous NSCLC. While the use of bevacizumab is developed, the contribution of bevacizumab maintenance to overall results has not been tested in a randomized setting. Additionally, maintenance treatment may add to the toxicity encountered. We report on a consecutive group of patients with adenocarcinoma subtype NSCLC who received bevacizumab plus chemotherapy, without bevacizumab maintenance. Efficacy and toxicity is reviewed and compared to the data of the literature. The decision to treat without bevacizumab maintenance in the period reported on was made because of

general safety concerns and was applied to all consecutive patients fulfilling criteria for receiving bevacizumab together with chemotherapy.

Patients and Methods

Previously untreated patients with advanced non-squamous NSCLC, with performance status (PS) 0-2, without uncontrolled hypertension, proteinuria, larger hemoptysis, or tumour close to large vessels received bevacizumab at 7.5 mg/kg intravenously together with carboplatin, area under curve (AUC 5), intravenously on day 1 and vinorelbine at 60 mg/m² orally at day 1 and at 80 mg/m² on day 8, repeated every three weeks for four courses without bevacizumab maintenance. Restrospectively, progression and mortality status was updated on April 10, 2013.

The literature was searched using PubMed and the Cochrane Library using key words: NSCLC, advanced NSCLC, bevacizumab, maintenance treatment.

Results

A total of 30 patients were included from July 2010 to July 2012. Age ranged from 31-71 years (median=60 years) and 29 (97%) had stage IV disease. Four patients (13%) had PS 2 and four others (13%) had brain metastases at the time of treatment commencement (Table I).The median lead time from diagnosis to treatment was 26 days. Eight patients (27%) completed one to two courses and 22 patients (73%) completed three to four courses. Two patients (7%) experienced minor bleeding episodes without the need for blood transfusion. Four patients (13%) discontinued induction treatment due to vascular complications: two developed pulmonary embolism, one had a deep venous thrombosis and one a bleeding episode of grade 3 with vaginal bleeding, hemoptysis, and epistaxis. Two patients (7%) had thrombocytopenia grade 3 and 4, respectively, without bleeding episodes. Grade 3 or 4 neutropenia occurred in eight cases (27%); three of these (10%) experienced febrile episodes. No toxic deaths occurred (Table II). A total of eight patients (27%) had partial remission (PR) and 13 (43%) had stable disease (SD), leading to a disease control rate of 70%. Three patients (10%) were alive at the time of data lock. Response rates and median OS and PFS were 31%, 8.8 months and 4.5 months in patients with PS 0-1 compared to 0%, 2.6 months and 1.2 months, respectively for those with PS 2. The one-year survival rate for patients with PS 0-1 was 42% (Figure 1).

Discussion

The response rate (RR) of 31% in patients with PS 0-1 observed in the current patient group without bevacizumab maintenance is consistent with findings in the literature using treatment including bevacizumab maintenance. However, it is recognized that the current study is small and

Table I. *Characteristics of 30 patients with advanced non-small cell lung cancer who received carboplatin/vinorelbine/bevacizumab without bevacizumab maintenance.*

Patient characteristics	No. (%)
Gender	
Male	11 (37)
Female	19 (63)
Median age (range) years	60 (31-71)
Histology	
Adenocarcinoma	29 (97)
Other	1 (3)
Smoking	
Active	11 (37)
Previous	11 (37)
Never	6 (20)
Unknown	2 (7)
Performance status (PS)	
0	10 (33)
1	14 (47)
2	4 (13)
Unknown	2 (7)
TNM stage	
IIIB	1 (3)
IV	29 (97)
Metastatic sites (some pttS had >1 site)	
Lung	15 (50)
Liver	6 (20)
Brain	4 (13)
Bone	12 (40)
Adrenal	5 (16)
Other	2 (7)
None	0 (0)

retrospective, while the E4599 and AVAiL trials are large prospective randomized trials. Hence, direct comparison is obviously hampered. The RR was 34.1% and 30.4% in the AVAiL trial with doses of bevacizumab at 7.5 mg/kg and 15 mg/kg, respectively (3) while the E4599 trial found a RR of 35% (2). The PFS of 4.5 months in this study without maintenance was lower than the 6.7 months and 6.5 months with bevacizumab in the lowdose and highdose groups, respectively, reported in the AVAiL trial (3). Similarly, the E4599 trial had a PFS of 6.6 months for patients with adenocarcinoma subtype (4). This suggests improved PFS with bevacizumab maintenance, or could reflect a prognostically worse patient group in the current study in which brain metastasis was not an exclusion criterion. The median OS of 8.8 months in the current study was also lower than the two pivotal randomized trials which reported an OS of 13.4 and 13.6 months in the two non-squamous groups receiving bevacizumab in AVAiL (5) and 14.2 months for those with adenocarcinoma subtype in E4599 (4). These findings regarding OS and PFS may reflect higher activity of chemotherapy with bevacizumab when it is used with

Table II. Toxicity in 30 patients with advanced non-small cell lung cancer who received carboplatin/vinorelbine/bevacizumab without subsequent bevacizumab maintenance.

Toxicity \geq grade 3	No. (%)
Leucocytopenia	7 (23)
Neutropenia	7 (23)
Febrile neutropenia	3 (10)
Trombocytopenia	2 (7)
Bleeding episodes	2 (7)
Neurotoxicity	1 (3)
Pulmonary embolism	1 (3)
Deep venous thrombosis	2 (7)

A patient could have more than one episode with haematologic toxicity. There was no nausea or nephrotoxicity of grade 3 or more.

bevacizumab maintenance, or reflect the somewhat higher activity of cisplatin which was used in the randomized trials compared to carboplatin used in the current study. Inclusion of patients with brain metastases may also aggravate general prognosis in the current study. With respect to the toxicity encountered, the frequencies of bleeding and thromboembolic complications were consistent with previous reports. Dansin *et al.* observed 3.6 % bleeding events of grade 3 or more (6) while Crinó *et al.* recorded 8% thromboembolic complications (7). These two studies were based on data from the same 2,212 patient cohort. The SAiL study reported the risk of bleeding of grade 3 or more to be higher with the bevacizumab maintenance treatment than with the induction treatment, at 2.3% versus 1.1%, respectively (7). Whether this is due to tumour necrosis during treatment or due to bevacizumab is uncertain. The risk of all grade bleeding was greater during induction treatment but almost all (88.6%) resolved or improved, suggesting that it might not be necessary to discontinue treatment with bevacizumab but rather to discontinue usage temporarily. With respect to risk factors for bleedings, no correlation between any grade bleeding and centrally located tumours were reported, but there was a correlation between any grade bleeding and cavitating tumours. No episodes of pulmonary haemorrhage (PH) occurred in the current study, although this is a well-known serious side-effect. The risk of developing life-threatening PH in patients with NSCLC is greater with histology of squamous cell carcinoma (8) which is an exclusion criterion for treatment with bevacizumab. The risk for grade 3 or more PH varies from 0.7% to 1.9% (2, 3, 6, 7) compared to 0.2% to 0.6% (2, 3) for treatment without bevacizumab. No correlation has been reported between clinical or radiological features (including cavitation and central tumour location) and development of PH (9). Cerebral bleeding did not occur in our patient group, although some patients had cerebral metastases. In contrast,

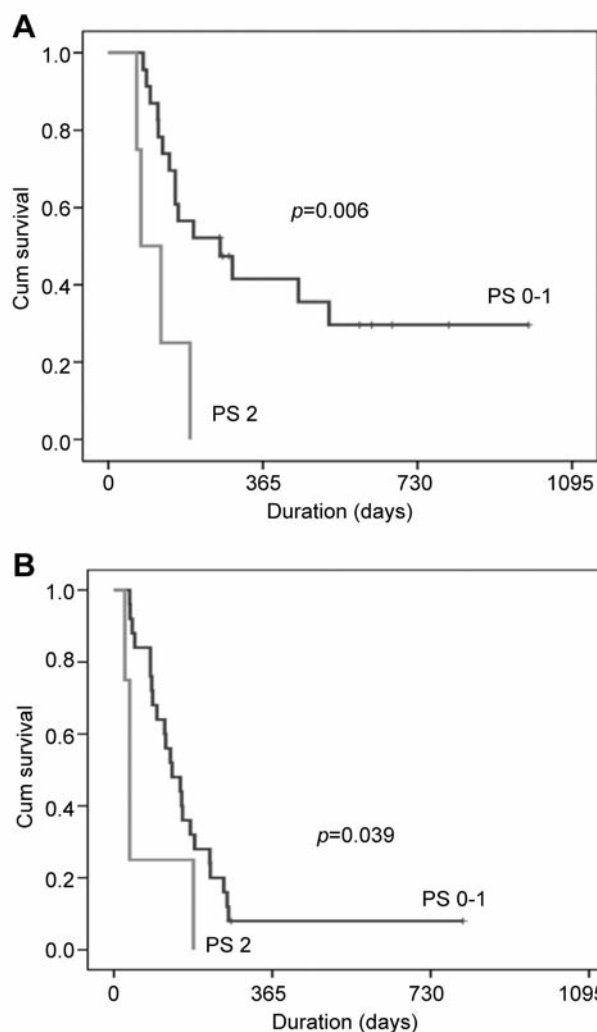


Figure 1. KaplanMeier estimates of overall survival (A) and progression-free survival (B) in 30 patients with advanced non-small cell lung cancer who received induction treatment of carboplatin/vinorelbine/bevacizumab without subsequent bevacizumab maintenance. Median OS in PS 0-1 patients is 8.8 months, 1-year survival 42%, and median PFS 4.5 months.

the presence of brain metastases was an exclusion criterion in the E4599 and AVAiL studies. The risk of spontaneous cerebral bleeding of grade 3 or more in patients with NSCLC is reported to be 0.1% (10). A pooled analysis found an overall rate of cerebral haemorrhage in patients treated with bevacizumab to be 0.8% to 3.3% and concluded that bevacizumab was not associated with increased risk of cerebral bleeding in patients with known brain metastases (11). In the SAiL study, the risk of cerebral bleeding of grade 3 or more, when treated with bevacizumab, was only 0.1% (7). Hence, treatment with bevacizumab in cases of known brain metastases is also approved according to the guidelines from National Cancer Center Network (12) and the European

Medicines Agency (13). A meta-analysis of four randomized clinical trials including 2200 patients showed a higher risk of severe haematological toxicities of grade 3 or more when bevacizumab was added to the therapy (14). There was, however, no observed higher risk of developing anaemia, thrombocytopenia or thromboembolic events with the addition of bevacizumab.

Conclusion

Thromboembolic complications may occur during treatment with bevacizumab and high awareness of such complications is thus necessary, which also holds true with respect to strict patient selection. The treatment without bevacizumab maintenance in the current study did not lead to markedly lower complication rates than currently reported from prospective trials using bevacizumab maintenance following induction treatment. Bevacizumab treatment yielded favourable PFS and OS in previous large randomized studies using bevacizumab maintenance after induction treatment. In spite of similar response rates, the somewhat lower median OS and PFS in the current retrospective study may be due to lack of bevacizumab maintenance, to the patient group having poor prognostic features such as brain metastases, or to stochastic variation. The poor outcome for patients with PS 2 suggests that this regimen is not a feasible treatment option for that particular group, although the data are limited. The impact of bevacizumab maintenance on the general results should be evaluated in randomized settings. Research on predictive markers for the use of bevacizumab and for predicting thromboembolic episodes are needed in order to improve results.

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