2014

Is Bevacizumab (Avastin) Safe and Effective as Adjuvant Chemotherapy for Adult Patients With Stage IIIb or IV Non-Small Cell Lung Carcinoma (NSCLC)?

Ashley R. De Kleine
Philadelphia College of Osteopathic Medicine, ashleyde@pcom.edu

Is Bevacizumab (Avastin) Safe and Effective As Adjuvant Chemotherapy For Adult Patients With Stage IIIb or IV Non-Small Cell Lung Carcinoma (NSCLC)?

Ashley R. De Kleine, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not bevacizumab (avastin) is safe and effective as adjuvant chemotherapy for adult patients with stage IIIb or IV non-small cell lung carcinoma (NSCLC).

STUDY DESIGN: Review of three randomized controlled trials (RCT) published in 2006, 2009, and 2011, all English language.

DATA SOURCES: Two randomized, double-blind, controlled clinical trials comparing bevacizumab to placebo as adjunctive chemotherapy, and one RCT comparing bevacizumab as adjunctive chemotherapy versus the use of no adjunctive chemotherapy. All articles were found using PubMed, Medline, and OVID.

OUTCOMES MEASURED: Overall survival (OS) and progression-free survival (PFS) were measured. OS was defined as time from randomization to death from any cause. PFS was defined as time from randomization to first documented disease progression or death on study treatment, whichever occurred first. Event-time distributions were estimated using the Kaplan-Meier method.

RESULTS: Herbst et al[2] and Reck et al[6] compared traditional chemotherapy plus bevacizumab to traditional chemotherapy plus placebo, and Sandler et al[3] compared traditional chemotherapy plus bevacizumab to traditional chemotherapy alone. Herbst et al[2] failed to find a significant difference in OS or PFS between subjects using adjuvant bevacizumab and those using traditional chemotherapy. Reck et al[6] was unable to assess OS; however, the investigators reported that PFS was significantly improved with the addition of bevacizumab to traditional chemotherapy. Sandler et al[3] established that the addition of bevacizumab to traditional chemotherapy has statistically significant survival benefits in patients with NSCLC.

CONCLUSIONS**:** From the research performed and results obtained, the evidence is inconclusive and conflicting to support the use of bevacizumab as adjuvant chemotherapy for stage IIIb or IV NSCLC. With inconsistencies and differing results among the three RCTs, further research would be helpful to confirm or negate the question of whether bevacizumab is actually beneficial as adjuvant therapy. In addition to researching the efficacy and safety of bevacizumab as adjuvant chemotherapy, it would be advantageous to study the efficacy and safety of bevacizumab as monotherapy. Further research is warranted to obtain more conclusive data.

KEY WORDS: Non-small cell lung cancer, Avastin, Bevacizumab, adjuvant chemotherapy

INTRODUCTION

Malignant epithelial cells that form in the lung tissue cause non-small cell lung carcinoma (NSCLC), with the most common types being squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLC may present as an incidental finding on chest imaging or with symptoms due to either local invasion or compression of adjacent thoracic structures. Common symptoms, which may be indicative, but are neither specific nor diagnostic for lung cancer, include hemoptysis, worsening cough, chest pain, weight loss, malaise, dyspnea, and/or hoarseness.[1] As a class, NSCLCs are reasonably unresponsive to chemotherapy and radiation therapy. Nevertheless, the addition of bevacizumab as adjunctive treatment to traditional chemotherapy, has been investigated as an option for patients with NSCLC that is refractory to treatment.[1] This paper evaluates three randomized controlled trials (RCT) comparing the efficacy and safety of bevacizumab (avastin) as adjuvant chemotherapy for adult patients with stage IIIb or IV NSCLC.

NSCLC is a major cause of illness, disability, and death. Lung cancer is the leading cause of death worldwide, with more than 85% of lung cancers being NSCLC.[1,2,3] Due to vague presenting symptoms or incidental findings on imaging, around 75% of NSCLC patients are initially diagnosed with advanced metastatic disease.[2] National cancer care expenditure for lung cancer is an estimated $12.12 billion, with lost time and economic productivity being greatest for adults aged 20 years and older.[4] Lung cancer diagnoses account for innumerable healthcare visits each year; however, there are no exact estimates for small cell lung carcinoma versus NSCLC. It is estimated that around 228,000 newly diagnosed cases of lung cancer are treated each year, accounting for about 14% of cancer diagnoses.[1,5] Further, around 159,000 lung cancer deaths occurred in the United States in 2013 alone.[1] The commonality of the disease coupled with

staggering healthcare costs and time is indicative of the fact that NSCLC treatment is a topic that is relevant to both patients and the physician assistant practice.

The most important risk factor related to the development of NSCLC is smoking, including both first- and second-hand smoke. Other risk factors include environmental exposures, such as radon, asbestos, and air pollution, and a personal or family history of lung cancer. Although lung cancer may present as an incidental finding on imaging, the most common presenting symptoms include worsening cough, chest pain, or hemoptysis.[1] Due to the fact that NSCLC frequently presents as metastatic disease, clinicians also look for signs of distant metastases, such as malaise, weight loss, dyspnea, and hoarseness.[1]

Vascular endothelial growth factor (VEGF), which is commonly associated with NSCLC, promotes tumor growth and progression via angiogenesis. Bevacizumab is a monoclonal anti-VEGF antibody that inhibits angiogenesis, thereby slowing the growth of carcinoma. Bevacizumab has shown clinical improvement in various cancers, including NSCLC.[2] Consequently, bevacizumab as adjunctive treatment has not been studied comprehensively as to which combination of traditional chemotherapy would provide the most benefit, nor has it been studied extensively as a monotherapy for NSCLC.

There are several therapeutic treatment options available for patients with NSCLC; yet, results of standard treatment are often poor because most NSCLC diagnoses present as metastatic disease, rather than localized.[2] In NSCLC, surgery is the most theoretically curative treatment for patients. Postoperative chemotherapy and/or radiation therapy may provide additional benefit. Patients who present with advanced stage disease have shown improvement from chemotherapy and/or epidermal growth factor receptor (EGFR) kinase inhibitors. [1] The standard treatment options for patients with stage IIIb NSCLC include postoperative

chemotherapy, combination chemotherapy and radiation therapy, and/or radiation therapy alone. The first-line treatment options for patients with stage IV NSCLC are combination chemotherapy, combination chemotherapy with bevacizumab, or EGFR tyrosine kinase inhibitors. Other traditional treatment options for stage IV NSCLC include endobronchial laser therapy and/or brachytherapy or external-beam radiation therapy.[1] Each option mentioned plays a role in treatment depending on the stage and histologic grade of the NSCLC. The use of bevacizumab has been shown to be effective in the treatment of grade IIIb and IV NSCLC when combined with specific types of adjuvant chemotherapy. This selective evidence-based medicine (EBM) review evaluated RCTs to examine the effectiveness of bevacizumab as adjuvant chemotherapy in the treatment of NSCLC.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not bevacizumab (avastin) is safe and effective as adjuvant chemotherapy for adult patients with stage IIIb or IV NSCLC.

METHODS

Specific selection criteria for the RCTs were used for this EBM review. The population chosen was adults $\geq$ 18 years old with stage IIIb or IV NSCLC. The intervention utilized in each study was bevacizumab adjuvant chemotherapy. Comparisons were made between traditional chemotherapy, such as paclitaxel-carboplatin, erlotinib, or cisplatin-gemcitabine, plus bevacizumab and traditional chemotherapy plus placebo or chemotherapy alone. Outcomes measured were based on patient oriented evidence that matters (POEMs), specifically, the overall survival (OS) and progression-free survival (PFS). The study types included three RCTs comparing bevacizumab adjuvant chemotherapy to traditional treatment options.

Key words used in the searches were “non-small cell lung cancer,” “avastin,” “bevacizumab,” and “adjuvant chemotherapy.” All articles were published in peer-reviewed journals and in the English language. The author researched the articles via PubMed, Medline, and OVID. Articles were selected based on their relevance to the author’s EBM question, in addition to the inclusion of study outcomes that mattered to the patients (POEMs). Studies that were RCTs published after 1996 and studies with patients over the age of 18 years old with stage IIIb or IV NSCLC were included. Studies with patients under the age of 18 years old and/or with stage I through IIIa NSCLC were excluded. Additional demographics and characteristics related to each study are included in Table 1. The statistics used in the studies to evaluate the patient outcomes included ABI, HR, NNT, and RBI.[2,3,6]

OUTCOMES MEASURED

The outcomes measured were based on OS and/or PFS. OS was defined as time from randomization to death from any cause. PFS was defined as time from randomization to first documented disease progression or death on study treatment, whichever occurred first. Outcomes were evaluated using stratified Cox proportional hazard models to estimate hazard ratios, comparing how often survival occurred with the addition of bevacizumab to how often it occurred with traditional chemotherapy alone. Event-time distributions were estimated using the Kaplan-Meier method.[2,3,6]

RESULTS

The data collected from the Sandler et al and Reck et al RCTs was in dichotomous form, while data collected from the Herbst et al RCT was in continuous form. Herbst et al[2] and Reck et al[6] compared traditional chemotherapy plus bevacizumab to traditional chemotherapy plus placebo, while Sandler et al[3] compared traditional chemotherapy plus bevacizumab to traditional

chemotherapy alone.

Table 1 – Demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Herbst, 2011[2]	Double-blind RCT	636	18+ y/o	Patients 18+ y/o who had SCC and had received neoadjuvant or adjuvant therapy for stage I-IIIa disease with ECOG performance score of 0 to 1	Pts with an MI within the past 6 mo, UA, CHF, arrhythmia, PVD, uncontrolled HTN, h/o of hemoptysis, presence of a tumor invading blood vessels, bleeding diathesis, another invasive CA within 5 yrs prior to randomization, current use of aspirin or NSAIDs, previous tx with anti-EGFR or anti-VEGF agents, surgery 28 d before study	0	Erlotinib plus bevacizumab
Reck, 2009[6]	Double-blind RCT	1043	18+ y/o	Patients 18+ y/o who had stage IIIb or IV NSCLC with ECOG performance score of 0 to 1	Pts with SCLC, h/o hemoptysis, CNS metastasis, h/o thrombotic d/o, current use of aspirin, CVD, uncontrolled HTN, surgery 4 wk before study, presence of a tumor invading blood vessels	0	Cisplatin and gemcitabine plus bevacizumab
Sandler, 2006[3]	RCT	878	18+ y/o	Patients 18+ y/o who had stage IIIb or IV NSCLC with ECOG performance score of 0 to 1	Pts with hemoptysis, CNS metastasis, bleeding diathesis, current use of NSAIDs, major surgery 28 d before enrollment, CVD, uncontrolled HTN	0	Paclitaxel and carboplatin chemotherapy plus bevacizumab

Herbst et al[2] conducted a randomized controlled double-blind clinical trial that involved enrolling 636 patients at 177 study sites in 12 countries from June 8, 2005 to April 16, 2008. 319 patients were randomly assigned to the traditional chemotherapy (erlotinib) plus bevacizumab group, and 317 patients were assigned to the erlotinib plus placebo group. Median follow-up time for patients in either group was 19 months after initial enrollment date. The investigators reported no difference in OS between the groups, as median OS was around 9.2 to 9.3 months in both placebo and bevacizumab groups. Hazard ratios were estimated through use of an unstratified Cox model, which produced a HR of 0.97 with a 95% CI (0.80-1.18) and p-value of 0.7583 (Table 2).[2] PFS appeared to differ significantly among the bevacizumab and placebo groups in this study. Herbst et al[2] reported results as 3.4 months in the bevacizumab group compared to 1.7 months in the control group. However, results were not reported as statistically significant due to the fact that fixed-sequence testing was used in order to control the overall type I error rate.[2]

Table 2 – Efficacy of erlotinib plus bevacizumab in comparison to erlotinib plus placebo measured via overall survival hazard ratio[2]

	Bevacizumab Median OS, months (IQR)	Placebo Median OS, months (IQR)	Hazard Ratio	P-value	95% CI
Overall Survival (OS)	9.2, (3.8 – 20.2)	9.3, (4.1-21.6)	0.97	0.7583	(0.80-1.18)

Reck et al[6] conducted a RCT that involved randomly assigning 1,043 patients at 150 study sites in 20 countries between February 2005 and August 2006 to three different groups. 347 patients were randomly assigned to the traditional chemotherapy (cisplatin-gemcitabine) plus placebo group, 345 patients were assigned to the cisplatin-gemcitabine plus low-dose bevacizumab group, and 351 patients were assigned to the cisplatin-gemcitabine plus high-dose bevacizumab group. Traditional chemotherapy was administered every three weeks for up to six

cycles, and bevacizumab or placebo was administered every three weeks until either the disease progressed or adverse events were intolerable. The investigators reported insufficient follow-up time for OS analysis.[6] Conversely, a considerable difference in PFS was noted in both of the low- and high-dose bevacizumab groups compared to the control. Median PFS was around 6.7 months in the group assigned to low-dose bevacizumab and 6.5 months in the group assigned to high-dose bevacizumab, compared to 6.1 months in the chemotherapy plus placebo group. Hazard ratios were determined via Kaplan-Meier estimates, which produced a low-dose bevacizumab HR of 0.75 with a 95% CI (0.62-0.91), and p-value of 0.003. The high-dose bevacizumab HR was 0.82 with a 95% CI (0.68-0.98), and p-value 0.03 (Table 3). [6]

Table 3 – Efficacy of cisplatin and gemcitabine plus either low- or high-dose bevacizumab in comparison to cisplatin and gemcitabine plus placebo measured via progression-free survival hazard ratio[6]

	Low-dose Bevacizumab Median PFS	High-dose Bevacizumab Median PFS	Placebo PFS	Hazard Ratio		P-Value		95% CI	
				Low-Dose	High-Dose	Low-Dose	High-Dose	Low-Dose	High-Dose
Progression-Free Survival (PFS)	6.7 months	6.5 months	6.1 months	0.75	0.82	0.003	0.03	(0.62-0.91)	(0.68-0.98)

Sandler et al[3] conducted a randomized controlled double-blind clinical trial that involved enrolling 878 patients from July 2001 to April 2004. 434 patients were randomly assigned to the traditional chemotherapy (paclitaxel-carboplatin) plus bevacizumab group, and 444 patients were assigned to the paclitaxel-carboplatin alone group. The traditional chemotherapy was administered every three weeks for six cycles, and bevacizumab was administered every three weeks until either the disease progressed or adverse events were intolerable. The investigators reported a considerable difference in OS between the groups. Median OS was around 12.3 months in the group assigned to traditional chemotherapy plus bevacizumab, compared to 10.3

months in the chemotherapy-alone group. Hazard ratios were determined via Kaplan-Meier estimates, which produced a HR of 0.79 with a 95% CI (0.67-0.92) and p-value of 0.003.[3] PFS also appeared to be statistically significant when comparing the bevacizumab and chemotherapy-alone groups in this study. Sandler et al[3] reported results as 6.2 months in the bevacizumab group compared to 4.5 months in the control group. Hazard ratios were estimated by use of an unstratified Cox model, which produced a HR of 0.66 with a 95% CI (0.57-0.77) and p-value < 0.001 (Table 4).[3]

Table 4 – Efficacy of paclitaxel and carboplatin plus bevacizumab in comparison to paclitaxel and carboplatin alone measured via overall survival hazard ratio[3]

	Bevacizumab 1-year OS, 2-year OS	Chemotherapy alone 1-year OS, 2-year OS	Hazard Ratio	P-value	95% CI
Overall Survival (OS)	51%, 23%	44%, 15%	0.79	0.003	(0.67-0.92)

Table 5 shows relative benefit increase (RBI) for overall survival, which was statistically significant in both Herbst et al[2] and Sandler et al[3] studies, with the addition of bevacizumab to traditional chemotherapy. For the Herbst et al[2] study, the RBI was calculated to be 32% and absolute benefit increase was 11%. Numbers needed to treat (NNT) was calculated as 9, meaning that nine patients need to be treated with bevacizumab compared to traditional chemotherapy alone in order to have one person have improved overall survival. For the Sandler et al[3] study, the RBI was calculated to be 16% and absolute benefit increase was 7%. NNT was calculated as 14, meaning that fourteen patients need to be treated with bevacizumab compared to traditional chemotherapy alone in order to have one person benefit from this type of treatment.

Table 5 – Benefit of bevacizumab on overall survival

	CER	EER	RBI	ABI	NNT
Erlotinib plus bevacizumab in comparison to erlotinib plus placebo (Herbst et al)[2]	34%	45%	32%	11%	9
Paclitaxel and carboplatin plus bevacizumab in comparison to paclitaxel and carboplatin alone (Sandler et al)[6]	44%	51%	16%	7%	14

Adverse events (AE) were also measured in each of the RCTs. Herbst et al[2] reported 42% of the bevacizumab group compared to 36% of the control group with a serious AE ≥ grade 3. Reck et al[6] reported similar findings between the bevacizumab group and the control group with regards to AEs. The investigators of this study reported 81% of the high-dose bevacizumab and 76% of the low-dose bevacizumab compared to 75% of the control group with a serious AE ≥ grade 3.[6] Finally, Sandler et al[3] reported several significant AEs that occurred more often in the bevacizumab group, compared to the control group (Table 6).

Table 6 – Adverse events reported with administration of bevacizumab[3]

Adverse Event	Bevacizumab Group # of patients (%)	Control Group # of patients (%)	P-Value
Neutropenia	109 (25.5)	74 (16.8)	0.002
Hypertension	30 (7)	3 (0.7)	<0.001
Proteinuria	13 (3.1)	0 (0)	<0.001
Headache	13 (3.0)	2 (0.5)	0.003
Bleeding event	19 (4.4)	3 (0.7)	<0.001

Table 7 shows relative risk increase (RRI) for adverse events (AE), which was statistically significant in the Sandler et al[3] study. Numbers needed to harm (NNH) was calculated for each significant AE. The most significant result, headache, had an NNH that was calculated as 40, meaning that forty patients need to be treated with bevacizumab compared to traditional chemotherapy alone in order to have one person experience AE of headache.

Table 7 – Risk of bevacizumab on adverse events

	CER	EER	RRI	ARI	NNH
Neutropenia	16.8%	25.5%	52%	8.7%	11
Hypertension	0.7%	7%	900%	6.3%	16
Proteinuria	0%	3.1%	N/A	3.1%	32
Headache	0.5%	3%	500%	2.5%	40
Bleeding event	0.7%	4.4%	529%	3.7%	27

DISCUSSION

This systematic review investigated three RCTs for the safety and efficacy of bevacizumab as adjuvant chemotherapy for adult patients, 18 years of age and older, with stage

IIIb or IV NSCLC. The study by Herbst et al[2] failed to find a significant difference in OS or PFS between subjects using adjuvant bevacizumab and those using traditional chemotherapy. While the Reck et al[6] study was unable to assess OS; the investigators did find that PFS was significantly improved with the addition of bevacizumab to traditional chemotherapy. The study by Sandler et al[3] established that the addition of bevacizumab to traditional chemotherapy has statistically significant survival benefits in patients with NSCLC.

Bevacizumab is FDA approved to treat NSCLC, metastatic colorectal cancer, metastatic HER2 negative breast cancer, and metastatic renal cell carcinoma.[7] It is also approved for second-line treatment of glioblastoma. The drug has a black box warning for gastrointestinal perforations, wound healing complications, and hemorrhage.[7] Most importantly, fatal pulmonary hemorrhage has been reported in patients with NSCLC treated with chemotherapy plus bevacizumab.[7] This significant AE was demonstrated in a small percentage of patients in each of the RCTs, which is important when considering future studies.[2,3,6]

Limitations were present in each RCT, which affect their validity regarding the question of concern. Herbst et al[2] reported that crossover effects from using a potentially active chemotherapeutic agent, bevacizumab, were not monitored throughout the study. Furthermore, Herbst et al[2] utilized subsequent lines of therapy during follow-up more often in the control group than in the bevacizumab group, which most likely confounded the comparison of OS between the two groups. In both the Reck et al[6] and Sandler et al[3] studies, confounding variables such as favorable prognostic features of the patient population may have influenced the favorable outcome of increased OS and PFS. For example, Reck et al[6] revealed that the overall patient population was younger with a higher incidence of less severe stage IIIb NSCLC as compared to

similar studies regarding bevacizumab and NSCLC. Finally, each of the three RCTs acknowledged financial support by Genentech and Roche, the marketers of bevacizumab.[2,3,6]

CONCLUSION

From the research performed and results obtained, the evidence is inconclusive and conflicting to support the use of bevacizumab as adjuvant chemotherapy for stage IIIb or IV NSCLC. Herbst et al[2] found that the addition of bevacizumab to traditional chemotherapy (erlotinib) does not improve OS or PFS in NSCLC patients. However, Reck et al[6] found that the addition of bevacizumab to traditional chemotherapy (cisplatin-gemcitabine) significantly improves only PFS rates. Finally, Sandler et al[2] found that the addition of bevacizumab to traditional chemotherapy (paclitaxel-carboplatin) has statistically significant OS and PFS benefits.

With inconsistencies and differing results among the three RCTs, further research would be helpful to confirm or negate the question of whether bevacizumab is actually beneficial as adjuvant chemotherapy. More importantly, stricter guidelines should be applied to future research regarding patient population characteristics, as well as the addition of bevacizumab to one specific traditional chemotherapy. In addition to researching the efficacy and safety of bevacizumab as adjuvant chemotherapy, it would be advantageous to study the efficacy and safety of bevacizumab as monotherapy. Comparisons can be made between the use of the drug as an adjunctive treatment versus the use of the drug as a single drug treatment for NSCLC. Continued research on bevacizumab for NSCLC will be beneficial to patients who are refractory to initial treatments of the disease. Further research is warranted to obtain more conclusive data.

References

1. National Cancer Institute at the National Institutes of Health. Non-small cell lung cancer treatment (PDQ) – Health professional version. http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional. Accessed September 25, 2013.

2. Herbst RS, Ansari R, Bustin F, et al. Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): A double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9780):1846-1854. doi: 10.1016/S0140-6736(11)60545-X; 10.1016/S0140-6736(11)60545-X.

3. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542-2550. doi: 10.1056/NEJMoa061884.

4. National Cancer Institute at the National Institutes of Health. Cancer trends progress report – 2011/2012 update. http://progressreport.cancer.gov/doc_detail.asp?pid=1&did=2007&chid=75&coid=726&mid. Accessed September 25, 2013.

5. American Cancer Society. Cancer facts and figures 2013. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf. Accessed September 25, 2013

6. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol*. 2009;27(8):1227-1234. doi: 10.1200/JCO.2007.14.5466; 10.1200/JCO.2007.14.5466.

7. National Cancer Institute at the National Institutes of Health website. FDA approval for bevacizumab. http://www.cancer.gov/cancertopics/druginfo/fda-bevacizumab. Accessed December 1, 2013.