Targeted therapy of advanced non-small cell lung cancer: the role of bevacizumab

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Abstract: Lung cancer is the leading cause of cancer death in the United States. The majority of patients present with advanced stage disease, and treatment with standard cytotoxic chemotherapy agents have been shown to provide a modest improvement in survival, reduce disease-related symptoms, and improve quality of life. However, with standard chemotherapy treatments the prognosis is poor with the majority of patients dying in less than a year from diagnosis. Treatment with standard chemotherapy agents has reached a therapeutic plateau, and recent investigations have focused on therapies that target a specific pathway within the malignant cell or related to angiogenesis. The most promising of the targeted therapies are agents that target the process of angiogenesis. Bevacizuamab is a monoclonal antibody that binds to circulating vascular endothelial growth factor (VEGF)-A, and prevents binding of VEGF to vascular endothelial growth factor receptors, thus inhibiting activation of the VEGF pathway and angiogenesis. A recent phase III trial of first-line treatment of advanced non-small cell lung cancer revealed a statistically significant improvement in response, progression-free survival, and overall survival with the combination of bevacizumab and standard chemotherapy in comparison to standard chemotherapy alone. Bevacizumab is the only targeted therapy that has been shown to improve survival when combined with standard chemotherapy in the first-line setting.

Keywords: non-small cell lung cancer, bevacizuamab, chemotherapy, lung cancer

Introduction

In the United States, lung cancer is the leading cause of cancer deaths among both men and women, and it is estimated that in 2007 that more people will die of lung cancer than breast, colon, and prostate cancer combined (Jemal et al 2007). Approximately 85% will have the non-small cell histology, and two-thirds will present with advanced stage disease (Bulzebruck et al 1992; Govindan et al 2006). Advanced stage is generally defined as malignant involvement of the supraclavicular lymph nodes, malignant pleural or pericardial effusions, or metastases to a different lobe of the lung or another organ. The most frequent sites of metastases are the liver, bone, brain, or adrenal gland. In addition to the patients who present with advanced stage a high percentage of patients who present with early stage disease and undergo a potentially curative surgical resection will subsequently relapse with metastatic disease (Pisters and Le Chevalier 2005). The primary therapy in advanced stage and relapsed disease is chemotherapy. The current standard therapy for patients with a preserved functional status is double agent chemotherapy (Pfister et al 2004). The median survival with chemotherapy is 8–10 months, and the 1- and 2-year survival rates are 20%–30% and 10%–20%, respectively (Schiller et al 2002; Treat et al 2005). Most patients will receive 4–6 cycles of double agent chemotherapy. Extending the duration of double agent therapy has not been shown to improve survival, and results in a higher rate of treatment-related toxicity (Socinski et al 2002; Smith et al 2001). Additional treatment with single agent "maintenance" chemotherapy initiated after completion of double

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agent platinum therapy has not been shown to extend survival (Westeel et al 2005).

After initial treatment with chemotherapy all patients inevitably experience disease progression, generally in a median of 3–5 months after initiating chemotherapy. After completion of the initial chemotherapy treatment patients are observed and upon evidence of disease progression patients with a preserved functional status may be treated with additional therapy, often referred to as second-line therapy. There are currently three agents approved by the Food and Drug Administration (FDA) for second-line treatment advanced NSCLC: two cytotoxic agents, docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, USA) and pemetrexed (Alimta®; Eli Lilly and Company; Indianapolis, IN, USA), and erlotinib (Traceva®; Genentech, Inc., South San Francisco, CA and OSI Pharmaceuticals, Inc., Melville, NY, USA), an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) (Fossella et al 2000; Shepherd et al 2000, 2005; Hanna et al 2004). It appears from recent trials of first-line therapy that 40%–50% of patients will subsequently receive second-line therapy (Socinski et al 2002; Sandler et al 2006a). Patients with non-squamous histology, female gender, and a good functional status appear to be more likely to receive second-line therapy (Hensing et al 2005). The median survival and 1-year survival rate on second-line trials has been 6–8 months, and 30%, respectively (Fossella et al 2000; Hanna et al 2004; Shepherd et al 2000, 2005).

Given the modest survival of patients with advanced NSCLC, there has been significant interest in improving on standard therapies. Numerous clinical trials have compared treatment with two cytotoxic chemotherapy agents to treatment with three agents, and a recent meta-analysis revealed that the addition of third agent did not improve survival, but did result in increased toxicity (Delbaldo et al 2004). This has led to the belief that we have reached a "therapeutic plateau" in the treatment of advanced NSCLC with standard cytotoxic agents. There is significant interest in integrating the "targeted" therapies into the treatment of NSCLC. The hope is that advances in the understanding of the molecular biology of cancer cells will lead to therapeutic agents that specifically target the malignant processes within the cancerous cells, and have limited impact on the normal cellular processes. Thus, the newer targeted therapies may have increased efficacy as well as a lower rate of toxicity. Erlotinib and gefitinib (Iressa®; AstraZenca Pharmaceuticals, Wilmington, DE, USA), which specifically target the intra-cellular tyrosine kinase of the EGFR are examples of a targeted therapy in NSCLC.

There was initially tremendous enthusiasm that targeted therapy would improve first-line therapy in NSCLC; however, the initial enthusiasm has been tempered by the results of recent of phase III trials. Two target therapies, erlotinib and gefitinib revealed promising results as single agent activity in phase II trials (Fukuoka et al 2003; Kris et al 2003; Perez-Soler et al 2005). These led to the development of four phase III trials that compared standard chemotherapy to EGFR TKI therapy in combination with chemotherapy. Unfortunately these trials revealed that the addition of EGFR-TKI therapy did not improve response or survival (Giaccone et al 2004; Gatzemeier et al 2007; Herbst et al 2004, 2005c). Two phase III trials SPIRIT I and SPIRIT II, investigated the addition of bexarotene, a synthetic retinoid analog that preferentially binds to the rexinoid X receptor (RXR), to standard chemotherapy based on promising phase II data (Khuri et al 2001). Neither trial revealed an improvement in progression free survival or overall survival (Blumesnschein et al 2005; Jassam et al 2005). Phase III trials with matrix metalloproteinase inhibitors (MMPI) in combination with chemotherapy failed to revealed a survival benefit over standard chemotherapy as well (Smylie et al 2001; Bissett et al 2005). These trials have demonstrated that the integration of targeted therapy into first-line therapy for advanced NSCLC will be more difficult than initially anticipated.

Angiogenesis as a target

The development of new blood vessels, referred to as angiogenesis, is essential for solid tumor growth beyond 2–3 mm^3 (Folkman 1992). The physiologic role of angiogenesis in the healthy adults is limited to wound healing and the menstrual cycle (Ferrara et al 2003). A complex interaction of numerous stimulatory and inhibitory factors carefully regulates the process of angiogenesis. Tumors may remain dormant in an avascular phase; however, when the stimulating factors exceed the inhibitory factors an "angiogenic switch" occurs, and tumors initiate angiogenesis (Bergers and Benjamin 2003). Once the angiogenic switch occurs, a process of endothelial cell migration and proliferation, capillary tube formation, and the release of proangiogenic stimulating factors is initiated (Herbst et al 2005b). Vascular endothelial growth factor (VEGF)-A acts as the primary mediator of these processes (Bergers and Benjamin 2003). Other growth factors involved in this process include platelet-derived growth factor (PDGF), basic fibroblast growth factor, and transforming growth factor β (Ellis and Fidler

1996). Solid tumors may also develop the ability to secrete proangiogenic factors to support further angiogenesis and metastases (Folkman 1990; Herbst et al 2005b). Some tumor cells may express VEGF receptors, thus VEGF secretion may act as an autocrine as well as paracrine factor (Masood et al 2001). The development of these new blood vessels, often referred to as neovascularization, allows further growth of the primary tumor and the development of metastases by providing a pathway for tumor cells to circulate in the systemic circulation and establish additional metastases (Sandler et al 2004).

VEGF binds to two different tyrosine kinase receptors: VEGF receptor (VEGFR)-1 (also known as Flt-1), and VEGFR-2 (also known as KDR). VEGFR-1 and VEGFR-2 are predominantly located on endothelial cells, and receptor expression on normal tissues is low, and only up regulated during neovascularization (Shibuya et al 1990; Terman et al 1992; Brown et al 1993). VEGF binding to VEGFR-1 mediates angiogenesis, while binding to VEGFR-2 mediates angiogenesis and lymphangiogenesis (Ferrara et al 2003). There is third receptor, VEGR-3, which is predominantly involved in the regulation of lymphangiogenesis (Gerber and Ferrara 2005). VEGF has been associated the development of hyperpermeable, immature vasculature, which is typical of malignancy related angiogenesis (Dvorak et al 1995; Bates et al 2001; Ferrara et al 2003).

The role of angiogenesis in the progression of lung cancer is well established with multiple studies revealing that a high microvessel density is associated with the development of metastases and poor survival (Fontanini et al 1995; Lucchi et al 1997; D'Amico et al 1999; Yano et al 2000). High vascular density has also been associated with tumor progression (Ushijima et al 2001). VEGF is also known as vascular permeability factor, and may be associated with the development of brain edema, malignant pleural effusions, and ascites (Senger et al 1983; Yanagawa et al 1999; Ferrara et al 2003). The extensive preclinical data suggested that angiogenesis was critical to the pathogenesis and development of metastases in NSCLC.

There are currently multiple anti-angiogenesis agents being investigated in clinical trials for non-small cell lung cancer; however, the only one currently approved for the treatment of NSCLC by the Food and Drug Administration (FDA) is bevacizumab (Avastin®; Genentech, Inc South San Francisco, CA, USA). Bevacizumab is a recombinant humanized monoclonal antibody that binds to circulating VEGF preventing VEGF from binding to its receptors. Bevacizumab as a single agent has limited clinical activity, and in a phase I clinical trial in patients with solid tumors no responses were seen in the 23 patients evaluable for response (Gordon et al 2001). Twelve patients did have stable disease over the duration of the study. Thus, as single agent bevacizumab appears to be cytostatic; however, treatment with bevacizumab is synergistic with chemotherapy. In a pivotal phase III trial in metastatic colorectal cancer, patients treated with chemotherapy and bevacizumab had a superior survival to patients treated with the same chemotherapy (Hurwitz et al 2004). The synergistic effects of bevacizumab have been attributed to a reduction of vascular permeability and normalization of the tumor vasculature resulting in decreased interstitial pressure within the tumor. (Jain 2001) The reduction in the interstitial pressure is believed to result in improved delivery of cytotoxic therapy to the malignant cells (Jain 2001). Preclinical data indicates that treatment with VEGF-blocking therapy does increase the intratumoral uptake of chemotherapy (Wildiers et al 2003). Other possible mechanisms for the synergy with chemotherapy by bevacizumab include inhibiting re-population of the malignant cells in the interval between chemotherapy cycles, and augmenting the anti-angiogeneis effects of chemotherapy (Kerbel 2006).

Bevacizumab in the treatment of NSCLC

A phase I trial in patients with solid tumors revealed that bevacizumab could be safely combined with standard doses of carboplatin (Paraplatin®: Bristol-Meyers Squibb; Princeton, NJ, USA) and paclitaxel (Taxol®; Bristol-Meyers Squibb; Princeton, NJ, USA) (Margolin et al 2001). This led to the development of a randomized phase II trial in patients with advanced NSCLC. Ninety-nine patients were enrolled in this trial, and all patients received carboplatin area under the curve (AUC) = 6 using the Calvert equation, and paclitaxel 200 mg/m^2 every 3 weeks, and patients on the two investigational arms received bevacizumab 7.5 mg/kg (n = 32) or 15 mg/kg (n = 35) every 3 weeks until disease progression (Calvert et al 1989; Johnson et al 2004). Patients on all three arms received a median of 6 cycles of carboplatin and paclitaxel and patients on the low-dose and high-dose bevacizumab arms received a median of 8 and 10 doses of bevacizumab, respectively. Treatment with the high-dose bevacizumab resulted in statistically significant longer time to tumor progression in comparison to the control arm (7.4 months vs 4.2 months; p = 0.023). There was no significant difference in the time to tumor progression

between the carboplatin and paclitaxel arm and the low-dose bevacizumab arm (Table 1). Patients who received carboplatin and paclitaxel could receive single agent therapy with bevacizumab upon disease progression. Nineteen patients received second-line therapy with single bevacizumab, and five patients experienced stable disease. The median survival and one-year survival rate from the time of initiating bevacizumab therapy in this subgroup of patients was 10 months and 47%, respectively.

This trial revealed several notable bevacizumab related adverse events including hypertension, proteinuria, and episodes of hemorrhage. The episodes of hemorrhage consisted of two distinct clinical entities: minor mucocutaneous hemorrhage, predominantly epistaxis, and life threatening hemorrhage. Six patients experienced life threatening hemoptysis or hemorrhage, and four events were fatal. Squamous histology appears to be associated with the development of this complication since four of the 13 patients with squamous histology (31%) experienced severe hemorrhage versus two of the 54 (4%) of patients with non-squamous histology. Five of the six had cavitation at baseline or tumor necrosis during the therapy. Pulmonary hemorrhage may be associated with central location; however, central location may be a surrogate marker for histology since squamous cell tumors tend to be centrally located. Five of the six episodes occurred on the low-dose treatment arm, and events occurred early ($\leq$60 days) as well as late ($\geq$180 days); thus the events did not appear to be dose- or time-dependent.

If a subset analysis is performed in patients with the non-squamous histology (n = 79) it appears that the addition of bevacizumab to standard chemotherapy improves the response rate, time to tumor progression, and overall survival (Table 1). Based on the promising results of this phase II trial, the Eastern Cooperative Oncology Group (ECOG) initiated a phase II/III trail, ECOG 4599, comparing the standard therapy of carboplatin and paclitaxel to the combination of carboplatin, paclitaxel, and bevacizumab (15 mg/kg) every 3 weeks in patients with advanced stage non-squamous histology (Sandler et al 2006a). Exclusion criteria were: hemoptysis (defined as $\geq$1/2 a teaspoon of bright red blood); central nervous system metastases; clinically significant cardiovascular disease; medically uncontrolled hypertension; documented hemorrhagic diathesis or coagulopathy; anticoagulation therapy; regular use of aspirin (>325 mg daily), non-steriodal anti-inflammatory agents, or other agents known to inhibit platelet function. Patients could not have received radiation therapy within 21 days of enrollment or major surgery within 28 days of enrollment. Patients were required to have computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain within four weeks of enrollment to evaluate for brain metastases. Importantly, patients with centrally located tumors were not excluded. Of the 878 patients enrolled on the trial, 444 received carboplatin and paclitaxel and 434 received carboplatin, paclitaxel, and bevacizumab.

There was a statistically significant improvement in the response rate, progression-free survival, and overall survival in the bevacizumab containing arm (Table 2). This trial led the FDA to approve bevacizumab for the treatment of patients with advanced stage NSCLC with non-squamous histology in combination with carboplatin and paclitaxel. On a subgroup analysis no survival benefit was seen among women with treatment with bevacizumab despite a statistically significant improvement in response and progression free survival (Brahmer et al 2006). The test for a treatment gender interaction in a proportional hazards model for survival was statistically significant (p = 0.04). It is important to note that this trial was not statistically powered to evaluate the efficacy of bevacizumab in subgroups. The reasons

Table 1 Efficacy results of a three-arm randomized phase II trial with carboplatin and paclitaxel with and without bevacizumab Johnson et al (2004).

	All patients			**Patients with non-squamous histology**			
	C/P	**C/P + Bevacizumab 7.5 mg/kg**	**C/P+ Bevacizumab 15 mg/kg**		**C/P**	**C/P+ Bevacizumab 7.5 mg/kg**	**C/P+ Bevacizumab 15 mg/kg**
	n = 32	n = 32	n = 34		n = 25	n = 22	n = 32
Response (%)[a]	18.8	28.1	31.5	Response (%)	20	31.8	50
Median TTP (months)	4.2	4.3	7.4	Median TTP (months)	4.0	6.3	7.1
Survival (months)	14.9	11.6	17.7	Survival (months)	12.2	14.0	17.8

[a]Response as assessed by the investigator

Abbreviations: C/P, carboplatin and paclitaxel; TTP, time to progression.

Table 2 ECOG 4599 trial efficacy results (Sandler et al 2006a).

Parameter	C/P	C/P+B	Hazard ratio	p-value
Response (%)	15%	35%	Not applicable	<0.001
PFS (median)	4.5 months	6.2 months	0.66 (95% CI, 0.57–0.77	<0.001
Overall survival	10.3	12.3 months	0.79 (95% CI, 0.67–0.91)	0.003

Abbreviations: C/P, carboplatin and paclitaxel; C/P+B, carboplatin, paclitaxel, and bevacizumab; PFS, progression free survival; CI, confidence interval.

for the lack of a survival benefit in women are unclear, and potential explanations include an imbalance in unrecognized prognostic factors, statistical chances, or a true lack of benefit among women. There were no survival differences in survival related to gender on the previous trial of metastatic colorectal cancer (Hurwitz et al 2004). Until the potential relationship between gender and overall survival can be clarified, female patients who meet the eligibility criteria for the trial should be considered candidates for treatment with bevacizumab.

The bevacizumab-containing treatment arm did have a significantly higher rate of toxicity than the carboplatin and paclitaxel treatment arm. The bevacizumab containing arm had a higher rate National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 4 neutropenia (25.5% vs 16.8%, respectively; $p = 0.002$), thrombocytopenia (1.6% vs 0.2%, respectively; $p = 0.04$), and febrile neutropenia (5.2% vs 2.0%, respectively; $p = 0.02$). There was a higher rate of non-hematologic toxicity as well including grade 3–5 hypertension (7% vs 0.7%, respectively; $p < 0.001$), hemorrhage (4.4% vs 0.7%, respectively; $p < 0.001$), and grade 3 proteinuria (3.1% vs 0%, respectively; $p < 0.001$). There were seven hemorrhage-related deaths on the bevacizumab arm (pulmonary hemorrhage ($n = 5$), and gastrointestinal bleeding ($n = 2$). The other causes of death on the bevacizumab arm were: complications of febrile neutropenia ($n = 5$), cerebrovascular event ($n = 2$) and probable pulmonary embolism ($n = 1$). There were 15 treatment-related deaths on the bevacizumab arm versus two on the standard treatment arm ($p = 0.001$).

An exploratory retrospective analysis of the episodes of pulmonary hemorrhage occurring <150 days from initiation treatment was performed. (Sandler et al 2006b) This analysis used a case-control method in an attempt to identify radiographic and clinical risk factors for the development of severe pulmonary hemorrhage. Hemoptysis at baseline, and tumor cavitation were identified as probable risk factors for pulmonary hemorrhage. Central location was not identified as a risk factor. Given the small number of cases involved in this analysis a larger analysis which included patients from ongoing clinical trials may provide additional information about risk factors for pulmonary hemorrhage, and the relative risk associated with each risk factor.

In addition to these two trials, a third trial, known as AVAil (BO17704) has completed enrollment, and the preliminary results were presented at the American Society of Clinical Oncology meeting in June 2007 (Manegold et al 2007). This was a three arm trial designed to compare the efficacy of chemotherapy and two different doses of bevacizumab versus chemotherapy alone, and was not designed for a comparison of the efficacy of two different doses of bevacizumab. To be eligible for this trial patients were required to have non-squamous histology, a preserved functional status, and chemotherapy-naïve stage IIIB/IV or recurrent NSCLC. The exclusion criteria were: grade ≥2 hemoptysis; radiological evidence of tumor invasion of major blood vessels; brain metastases or spinal cord compression; uncontrolled hypertension; history of thrombotic or hemorrhagic disorders; and therapeutic anticoagulation within 10 days of the first treatment. The initial primary end-point was an improvement in overall survival with the combination of chemotherapy and bevacizumab versus chemotherapy alone; however, after enrollment on the trial had begun the trial was amended and the primary end-point was changed to progression-free survival.

One thousand and forty-three patients were enrolled on the trial, and patients were randomized to three arms: cisplatin (80 mg/m^2) on day 1 and gemcitabine 1250 mg/m^2 on days 1, 8 and placebo every 3 weeks ($n = 347$) or the same chemotherapy with either 7.5 mg/kg ($n = 345$) or 15 mg/kg ($n = 351$) every 3 weeks. Bevacizumab was continued until disease progression and no crossover to bevacizumab was allowed. Patients on the chemotherapy and bevacizumab arms experienced a statistically significant improvement in the progression-free survival in comparison to the pooled placebo; cisplatin, gemcitabine, and bevacizumab 7.5 mg/kg arm versus pooled placebo (hazard ratio [HR] = 0.75; 95% confidence Interval [CI] 0.62–0.91, $p = 0.0026$) and cisplatin, gemcitabine and bevacizumab 15 mg/kg versus pooled placebo (HR = 0.82; 95% CI 0.68–0.98, $p = 0.0301$). The median

progression-free survival time for cisplatin and gemcitabine; cisplatin, gemcitabine and bevacizumab 7.5 mg/kg; and cisplatin, gemcitabine, and bevacizumab 15 mg/kg were 6.1 months, 6.7 months, and 6.5 months, respectively. At the time of this analysis the protocol-specified number of events for fully powered survival analysis has not been reached. The rate of grade ≥3 neutropenia, febrile neutropenia hemorrhage, and pulmonary hemorrhage were similar in all treatment arms. The rate of grade ≥3 pulmonary hemorrhage and febrile neutropenia for the cisplatin and gemcitabine, cisplatin, gemcitabine, bevacizumab 7.5 mg/kg and 15 mg/kg arms was 0.3%, 1.2%, and 0.9%, respectively and 1%, 2%, and 2%, respectively. The final results of this trial should provide valuable toxicity data; however, the trial design may limit conclusions that can be made in regards to the survival benefit of bevacizumab and the relatively efficacy of the two doses of bevacizumab.

Second-line trials

Two phase II trials have investigated the role of bevacizumab in patients with non-squamous histology who have progressed after initial chemotherapy treatment. Neither of these trials included patients who had received prior bevacizumab therapy, and the eligibility criteria were similar to the criteria used in ECOG 4599. A phase I/II trial investigated the toxicity and efficacy of bevacizumab in combination with erlotinib, an oral EGFR-TKI in patients who had received at least one prior line of chemotherapy for NSCLC (Herbst et al 2005a). Forty patients were enrolled on this trial, and 22 (55%) had received ≥ two prior lines of chemotherapy. No dose-limiting toxicities were observed in the phase I portion, and the phase II dose was established as erlotinib 150 mg daily and bevacizumab 15 mg/kg every 3 weeks. The most common toxicities observed were rash, diarrhea, hematuria, and proteinuria. No significant myelosuppression was observed.

The combination demonstrated significant activity with eight patients (20%) experiencing partial response, and 26 patients (65%) experiencing stable disease as their best response. The median survival for the 34 patients on the phase II dose was 12.6 months, and the progression-free survival was 6.2 months. Nine patients were never-smokers (22.5%) which has been associated with a higher response rate to erlotinib (Pao et al 2004). EGFR mutations have also been associated with increased response to EGFR-TKI therapy, and 9 patients had sufficient paraffin-embedded tissue for EGFR mutational analysis (Lynch et al 2004; Paez et al 2004; Pao et al 2004). These 9 patients included 3 patients with partial response, 3 patients with stable disease, and 3 patients with progressive disease.

A 3-arm randomized phase II trial investigated the safety and activity of bevacizumab in the second-line setting (Fehrenbacher et al 2006). Patients with central lesions, cavitation, or lesion proximal to major blood vessels were excluded. One hundred and twenty patients were randomized to one of the three treatment arms; second-line chemotherapy alone (pemetrexed or docetaxel) (n = 41), second-line chemotherapy (pemetrexed or docetaxel) in combination with bevacizumab (n = 40), and erlotinib in combination with bevacizumab (n = 39). There was a trend toward improved progression free survival with the addition of bevacizumab to chemotherapy (HR = 0.66; 95% CI 0.38–1.16) and bevacizumab and erlotinib (HR = 0.72; 95% CI 0.42–1.23) in comparison to chemotherapy alone. The difference in progression-free survival and overall survival did not reach statistical significance, and due to the trial design it cannot be definitively determined if treatment with the bevacizumab results in superior survival to standard therapy in the second-line setting. The preliminary safety data indicates that the rate of grade 3–5 hemorrhage was 5.1%, and the overall rate of neutropenia was similar between the two chemotherapy treatment arms. This trial provides valuable safety data about the use of bevacizumab in the second-line setting, and the trend toward improvement on progression free survival is intriguing but is insufficient to recommend the use of bevacizumab in the second-line setting.

Special populations

The eligibility criteria for ECOG 4599 trial excluded a significant percentage of the advanced NSCLC population. On recent United States cooperative group trials or multi-center trials the prevalence of brain metastases was 8%–17% (Treat et al 2005; Wakelee et al 2006a). Previously, imaging of the brain was only recommended if there was a clinical suspicion of brain metastases (Pfister et al 2004). However, now that the presence or absence if brain metastases may impact the therapeutic decisions the rate of brain imaging may increase which in turn will lead to more patients who have brain metastases that are detected. Magnetic resonance imaging (MRI) is more sensitive than CT scans, and an increase in the use of MRI may lead to an increase in the prevalence of brain metastases as well (Schellinger et al 1999). Patients with brain metastases have been excluded from bevacizumab trials based on a single episode of central nervous hemorrhage in a patient with a brain metastases due to hepatocellular carcinoma on a phase I trial (Gordon et al 2001). Given the

prevalence of brain metastases there is significant interest in investigating the safety of bevacizumab in patients with brain metastases from NSCLC. A phase II trial (known as the PASSPORT trial) of bevacizumab in combination with first or second-line chemotherapy is currently enrolling patients. The primary end-point is the incidence of NCI grade ≥2 central nervous system hemorrhage, and secondary objectives will be overall survival and toxicity. The interval between completion of the radiation therapy for brain metastases and the initiation of bevacizumab containing therapy is required to be a minimum of four weeks, and the choice of systemic therapy is at the discretion of the treating physicians.

There is also significant interest in determining if bevacizumab therapy can be used safely in patients with squamous histology. The prevalence of squamous histology on recent ECOG trials is estimated to be approximately 20%, and the decision to exclude patients with squamous histology was based on the toxicity seen with 13 patients on the phase II trial (Johnson et al 2004; Wakelee et al 2006a). The current hypothesis for the pathogenesis of pulmonary hemorrhage is that bevacizumab therapy induces central necrosis or enlargement of a pre-existing cavitation. The combination of a rapid response and the immature blood vessels of the tumor may result in hemorrhage into the tumor cavity (Johnson et al 2004). Treatment with thoracic radiation therapy, a standard therapy for hemoptysis, may reduce the risk of patients with squamous histology developing pulmonary hemorrhage. A trial to investigate this treatment approach is currently in development. Another phase II trial (known as the BRIDGE trial) will treat patients with squamous histology with two cycles of carboplatin and paclitaxel, and then initiate bevacizumab in combination with carboplatin and paclitaxel for the remaining cycles of therapy. Patients will receive bevacizumab until disease progression. The hypothesis is that the risk of pulmonary hemorrhage will be decreased with the delayed initiation of bevacizumab. The primary end-point will be the incidence of grade ≥3 pulmonary hemorrhage.

Duration of bevacizumab therapy

The optimal duration of bevacizumab therapy is another important clinical question. Patients on ECOG 4599 continued treatment until disease progression. Of the 407 patients who initiated treatment with carboplatin, paclitaxel, and bevacizumab, 215 (53%) continued treatment with bevacizumab monotherapy, and of these 107 (50%) received greater than five cycles of bevacizumab monotherapy. Treatment with single agent bevacizumab may cause regression of vasculature and inhibit the growth of new blood vessels which could have cytostatic effects on tumor growth and extend the progression free survival. Clinical data about the single-agent activity of bevacizumab are limited. On the phase II trial 19 patients who received first-line therapy with carboplatin and paclitaxel did subsequently receive single agent bevacizumab upon disease progression (Johnson et al 2004). Five patients did experience stable disease. This is a very small cohort to base any decisions about the efficacy of single agent bevacizumab in NSCLC. The concerns about continuing the bevacizumab are the development of resistance, the longer duration of exposure to treatment related complications, and the potential development of cumulative toxicities. It is also possible that the majority of the benefit the bevacizumab therapy may be obtained in a defined duration, and continuous therapy is not necessary. Until data are available the standard practice is to continue the bevacizumab until disease progression as done in the ECOG 4599 trial.

Future directions

Given the improvement in survival seen with advanced disease there is significant interest in incorporating bevacizumab in the potentially curative treatments of adjuvant therapy for patients with resectable disease and chemoradiotherapy for patients with locally advanced disease. Recent trials have revealed a survival benefit to treatment with adjuvant cisplatin-based chemotherapy after complete resection (Arriagada et al 2004; Douillard et al 2005; Winton et al 2005). ECOG 1505 trial will compare cisplatin-based adjuvant therapy versus cisplatin-based therapy in combination with bevacizumab in patients with resected stage IB (tumors ≥4 cm) stage II, and stage III disease (Wakelee et al 2006b). Physicians will be able to select among three cisplatin-based chemotherapy combinations; however, the selection of the chemotherapy treatment will occur prior to randomization. Patients randomized to bevacizumab therapy will receive bevacizumab (15 mg/kg every 3 weeks) with the first dose of chemotherapy, and for a total duration of one year. A phase II trial (known as the BEACON trial) is investigating neoadjuvant treatment (pre-operative chemotherapy) with bevacizumab in combination with cisplatin and docetaxel in patients with resectable stage IB to IIIA NSCLC (Giaccone 2007). This trial will provide valuable data about the response rate of bevacizumab containing therapy in earlier stage disease.

A multi-center phase I/II trial investigating the role of bevacizumab with induction chemotherapy and concurrent

chemoradiotherapy is being coordinated by the University of North Carolina. Patients with squamous histology will be eligible, but patients with squamous histology that invade or abut major blood vessels will be excluded. The other inclusion or exclusion criteria were similar to ECOG 4599. Patients will receive carboplatin, paclitaxel, and bevacizumab for two cycles, and then will receive weekly carboplatin, paclitaxel, and bi-weekly bevacizumab (10 mg/kg) with concurrent thoracic radiotherapy to 74 Gy. If the initial cohorts tolerable toxicity profile, intermittent erlotinib with thoracic radiology will be integrated in the treatment. The schedule of erlotinib is Tuesday through Friday, and the initial cohort will receive 50 mg daily. The final planned cohort will receive erlotinib 150 mg daily. After completion of the thoracic radiation therapy patients will receive erlotinib 150 mg daily with bevacizumab 15 mg/kg every 3 weeks for 6 cycles. The erlotinib will be discontinued with the bevacizumab.

The Southwest Oncology Group (SWOG) is performing a phase I/II trial of bevacizumab, cisplatin and etoposide in combination with thoracic radiation for patients with unresectable stage IIIA/B disease (www.swog.org accessed 3/25/2007). Two different schedules of bevacizumab during thoracic radiation therapy will be investigated on this trial. Patients with squamous histology will be excluded if tumor cavitation is present or the tumor is located within 10 mm of a major blood vessel. The other eligibility criteria are similar to ECOG 4599. After completion of the concurrent chemoradiotherapy part of the trial the patients will receive consolidation therapy with docetaxel and bevacizumab with growth colony stimulating factor (G-CSF) support during the consolidation therapy. The primary end-point will be the rate of grade 4 or 5 hemorrhage, and the secondary end-points will progression free survival and overall survival.

There is significant interest in determining which patients are most likely to benefit from bevacizumab-based therapy and identifying molecular markers that are predictive of benefit of anti-angiogenesis therapy. An investigation of pretreatment biomarkers on ECOG 4599 revealed that VEGF levels did correlate with overall survival, and baseline intercellular adhesion molecule (ICAM) levels were prognostic for survival and response to chemotherapy (Dowlati et al 2006). A retrospective analyses of 813 patients with metastatic colorectal cancer treated on the trial by Hurwitz et al investigated if VEGF, thrombospondin-2, and microvessel density were prognostic factors and/or predictors of benefit from bevacizumab (Jubb et al 2006). Neither of the biomarkers or the microvessel density was significant prognostic or predictive factors. Future bevacizumab trials will likely incorporate a variety of correlative science questions to investigate for potential biomarkers predictive of bevacizumab benefit.

Conclusion

The ECOG 4599 trial demonstrated that the addition of bevacizumab to standard chemotherapy resulted in a statistically significant and clinically relevant improvement in overall survival. This pivotal trial confirmed the extensive preclinical data that inhibiting angiogenesis would be an effective treatment and the critical role VEGF has in the process of tumor growth and metastases in NSCLC. This led to the FDA to approve bevacizumab for treatment for patients with advanced NSCLC and non-squamous histology in combination with carboplatin and paclitaxel. Bevacizumab is the first and only targeted therapy to extend survival when combined with chemotherapy in the first-line treatment of advanced NSCLC. The carefully selected inclusion criteria limited enrollment to patients who were at lower risk for bevacizumab-related bleeding complications; however, even in this select population the bevacizumab containing treatment had a statistically significant higher rate of grade 3–5 hemorrhage than seen with standard therapy. Current trials will investigate the safety of bevacizumab in patient populations excluded from ECOG 4599, and the efficacy and safety of bevacizumab in early and locally advanced stage disease. As with any therapeutic advance, additional studies will be required to determine the optimal integration into the current treatment paradigms, the selection of patients who are most likely to benefit, and the selection of patients at lowest risk of toxicity.

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