Place in therapy review

Bevacizumab: the evidence for its clinical potential in the treatment of nonsmall cell lung cancer

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Abstract

Introduction: Lung cancer is the leading cause of cancer-related mortality. Platinum-based chemotherapy is the usual first-line treatment for advanced nonsmall cell lung cancer (NSCLC), although an efficacy plateau has been reached with this approach. Bevacizumab is a recombinant, humanized, monoclonal antibody to vascular endothelial growth factor, which inhibits tumor angiogenesis and is being evaluated as a different mechanism to improve outcomes in patients with stage IIIB/stage IV (metastatic) NSCLC.

Aims: To review the emerging evidence for the potential use of bevacizumab in stage IIIB/IV NSCLC.

Evidence review: Adding bevacizumab to carboplatin plus paclitaxel improves response rates and significantly prolongs time to disease progression, which translates into a significant extension of overall survival (median 2.3 months in one key study). Low levels of intracellular adhesion molecule-1 are associated with better response. Preliminary evidence suggests that combining bevacizumab with erlotinib could improve outcomes in patients relapsing following platinum-based chemotherapy. Episodes of bleeding (particularly pulmonary hemorrhage) are the predominant adverse events associated with bevacizumab, probably a result of tumor disintegration.

There is limited evidence that the high acquisition cost of bevacizumab unfavorably affects assessment of its cost effectiveness, although there are few other treatment options in these patients with poor prognosis.

Place in therapy: The encouraging results obtained with bevacizumab in patients with NSCLC are leading to its adoption in some treatment guidelines. Emerging evidence indicates improved outcomes when bevacizumab is added to carboplatin/paclitaxel in previously untreated patients with NSCLC, and when used with erlotinib in patients who have relapsed following platinum-based chemotherapy.

Key words: bevacizumab, evidence, nonsmall cell lung cancer

Core evidence place in therapy summary for bevacizumab in NSCLC

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Progression-free survival	Clear	Addition of bevacizumab to platinum-based doublet chemotherapy (carboplatin/paclitaxel) followed by bevacizumab monotherapy until disease progression significantly improves progression-free survival compared with chemotherapy alone in the first-line treatment of predominantly nonsquamous, "wet IIIB"/stage IV (metastatic), or recurrent NSCLC
Survival	Clear	Addition of bevacizumab to platinum-based chemotherapy (carboplatin/paclitaxel) followed by bevacizumab monotherapy until disease progression significantly improves overall survival compared with chemotherapy alone in the first-line treatment of nonsquamous, wet IIIB/stage IV, or recurrent NSCLC
Quality of life	No evidence	
Safety and tolerability	Substantial	Tumors characterized as having a squamous cell histology appear to be a major risk factor associated with bleeding. There is also an increased risk of hypertension, capillary leakage, and proteinuria, which is generally asymptomatic and not associated with renal dysfunction
Disease-oriented evidence		
Response rate	Clear	Addition of bevacizumab to platinum-based doublet chemotherapy (carboplatin/paclitaxel) followed by bevacizumab monotherapy until disease progression significantly increases the overall response rate compared with chemotherapy alone in patients with previously untreated wet IIIB/stage IV, or recurrent NSCLC
Economic evidence		
Cost effectiveness	Limited	Adding bevacizumab may not be cost effective in terms of cost per life-year gained

Scope, aims, and objectives

Bevacizumab (Avastin®; Genentech/Roche), a recombinant, humanized, monoclonal antibody directed against human vascular endothelial growth factor (VEGF), is indicated in the US for first-line treatment of nonsmall cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel (Anon. 2006).

This review summarizes the disease background, current therapy options, and unmet medical needs in NSCLC, and examines the current evidence for the use of bevacizumab in this indication. Various outcomes are evaluated, including response rates, time to progression, survival, and safety/tolerability profiles for bevacizumab in combination with platinum-based chemotherapy (carboplatin plus paclitaxel) or the small molecule HER-1/epidermal growth factor receptor (EGFR) inhibitor, erlotinib, in the treatment of stage IIIB with malignant pleural effusion (also known as "wet IIIB" disease) and stage IV (metastatic) NSCLC (excluding predominantly squamous cell tumors). Finally, the potential place in therapy for bevacizumab in NSCLC is discussed.

Methods

The English language medical literature was searched between April 21 and November 18, 2005 and again on January 11 and September 19, 2006, in the following databases:

- PubMed, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

- EMBASE, http://www.datastarweb.com

- Database of Abstracts of Reviews of Effects (DARE), National Health Service (NHS) Economic Evaluations Database (NHSEED), Health Technology Assessment (HTA), http://www.york.ac.uk/inst/crd/darehp.htm. All fields searched in all three databases together

- NHS HTA, http://www.ncchta.org

- National Guideline Clearinghouse, http://www.guideline.gov

- Cochrane Database of Systematic Reviews (CDSR), http://cochrane.org/index0.htm

- Clinical Evidence (BMJ), http://clinicalevidence.com

- EBM Reviews [American College of Physicians (ACP) Journal Club], http://www.acpjc.org

The search terms used were "bevacizumab AND lung OR NSCLC," and the cut-off dates were from the beginning of the database to the date of the search.

The proceedings of the following oncology society meetings were also searched for relevant abstracts, again using the search terms "bevacizumab AND lung OR NSCLC."

- American Society for Clinical Oncology (ASCO) 2003–2006

- American Association for Cancer Research (AACR) 2005, 2006

- European Society for Medical Oncology (ESMO) 2004

- World Congress on Lung Cancer (WCLC) 2003, 2005

- The Euopean Cancer Congress (ECCO) 2003, 2005

The levels of evidence identified from the literature searches are summarized in Table 1.

Table 1	Evidence base included in the review	
Category	**Number of records**	
	Full papers	**Abstracts**
Initial search	42	27
records excluded	24	14
records included	4	13
Search update, new records	0	9
records excluded	0	2
records included	0	7
Preclinical evidence	0	2
Level 1 clinical evidence (systematic review, meta analysis)	1[a]	1[b]
Level 2 clinical evidence (RCT)	2	4[c]
Level ≥3 clinical evidence		
trials other than RCT	1	12[d]
case reports		
Economic evidence	0	2

For definition of levels of evidence, see Editorial Information on inside back cover.
[a]National Comprehensive Cancer Network (NCCN) updated clinical practice guidelines in October 2005 to include bevacizumab combined with chemotherapy in the first-line treatment of advanced NSCLC.
[b]Meta analysis of thromboembolic events in five trials of chemotherapy ± bevacizumab in patients with breast cancer, colorectal cancer, and NSCLC.
[c]Three abstracts were superseded by the publication of the corresponding full papers.
[d]Six abstracts were superseded by the publication of the corresponding full paper.
NSCLC, nonsmall cell lung cancer; RCT, randomized controlled trial.

Disease overview

Epidemiology and risk factors

Lung cancer is estimated to be the second most common cancer in women (after breast cancer) and the second most common cancer in men (after prostate cancer). In addition, lung cancer is the leading cause of cancer-related death in both males and females (Jemal et al. 2005). One in 13 males and one in 18 females are expected to develop lung cancer at some point during their lives (Jemal et al. 2005). The majority of patients with lung cancer are 35–75 years of age, with a peak incidence between the ages of 55–65 years (Jemal et al. 2005).

Epidemiologic studies have demonstrated a clear causal relationship between tobacco exposure and the development of lung cancer. Smoking is responsible for ~90% of lung cancer cases, and changes in lung cancer incidence and mortality over time have paralleled changes in the prevalence of cigarette smoking. There is also evidence for a dose–response relationship between cigarette consumption and the development of lung cancer, and cessation of smoking leads to a progressive reduction in lung cancer risk over time (Shopland 1991; Sasco et al. 2004; Wakai et al. 2005).

Independent of smoking status, lung cancer risk is also increased by exposure to other carcinogens such as asbestos (Hodgson & Jones 1986; Kjuus et al. 1986; Mossman et al. 1990; Marsh & Mossman 1998) and exposure to radon gas (Radford 1985; Harley et al. 1986; Nero 1986; Samet 1989), which is formed from the natural decay of uranium found in varying quantities in rocks and soils.

Some individuals may have a genetic predisposition to developing lung cancer. Several lines of evidence support this hypothesis. Lung cancer risk appears to be increased in patients with chronic obstructive pulmonary disease (COPD), even after correction for cigarette consumption. As COPD appears to have a familial association, this suggests that some individuals may have an inherited genetic predisposition to developing both COPD and lung cancer (Sellers et al. 1990; Minna et al. 1991). In addition, first degree relatives of patients with lung cancer appear to have an increased risk of developing lung cancer, compared with unrelated controls (Tokuhata & Lilienfeld 1963; Ooi et al. 1986).

NSCLC histologic subtypes

Nonsmall cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for ~80% lung cancer cases, whereas small cell lung cancer (SCLC) accounts for the remaining 20% of cases (Rivera et al. 2001; Jemal et al. 2004). It is important to distinguish between SCLC and NSCLC as the distinction dictates treatment options.

NSCLC is divided into three histologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Fig. 1). Adenocarcinomas tend to be peripherally located and frequently metastasize before the symptoms of local disease are apparent. Squamous cell carcinomas have the strongest association with smoking of the NSCLC subtypes, and are usually centrally located, generally remain localized, and have a tendency to cavitate. Large cell carcinomas consist of large cells with abundant cytoplasm, large nuclei, and prominent nucleoli.

Lung tumors often exhibit two or more histologic patterns (Fraire et al. 1987). Sometimes the quality and nature of the tissue available for pathologic review can lead to a classification of "NSCLC not otherwise specified."

Traditionally, the distinction between different NSCLC subtypes has not guided treatment decisions. However, as will be discussed later, this is starting to change with the development of novel targeted agents such as bevacizumab.
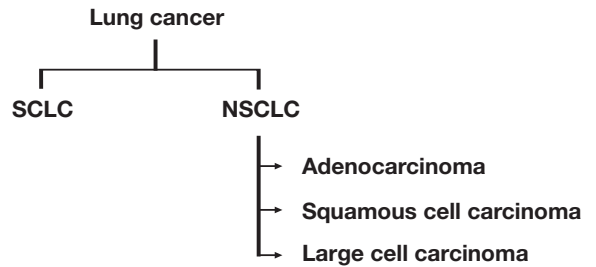

Fig. 1 | Lung cancer: histologic subtypes. NSCLC, nonsmall cell lung cancer; SCLC, small cell lung cancer

Disease staging

Once a histologic diagnosis of NSCLC has been established, it is important to establish the stage of the disease to determine the goals of therapy and treatment options. The TNM staging system is used to establish how localized or widespread the disease is. Information on the tumor (T) (i.e. how big it is and how far it has spread within the lung and to nearby organs), lymph node involvement (N), and the presence or absence of distant metastases (M) are collated, enabling an overall stage to be assigned (Mountain 1986). Criteria for T, N, and M assignments are summarized in Table 2. How T, N, and M assignments translate into an overall disease stage is explained in Table 3.

Table 2 | NSCLC: TNM staging (http://www.health-alliance.com/Cancer/Lung/staging.html)

Stage	Characteristics
Tumor (T)	
T1	Tumor ≤3 cm in greatest dimension, no proximal invasion
T2	Tumor >3 cm in diameter or involves the main bronchus or the tumor has caused partial collapse of the lung or the tumor has invaded the visceral pleura
T3	The tumor has invaded the chest wall, the mediastinal pleura, the diaphragm or the pericardium, or the tumor has caused the whole lung to collapse
T4	The tumor has invaded the mediastinum or there is malignant pleural effusion
Nodes (N)	
N0	No nodal involvement
N1	Involvement of the lymph nodes nearest the affected lung
N2	Involvement of mediastinal lymph nodes on the same side of the chest as the affected lung or the lymph nodes just under where the windpipe branches off to each lung
N3	Involvement of nodes on the opposite side of the chest to the affected lung or involvement of nodes above either of the collar bone bones
Metastasis (M)	
M0	No signs of tumor spread to another lobe or any other distant metastasis
M1	Tumor spread to another lobe of the lung or distant metastases

Table 3	Overall staging based on TNM groups (http://www.health-alliance.com/Cancer/Lung/staging.html)				
Overall stage	**T**	**N**	**M**	**Operable**	**5-year survival**
IA	T1	N0	M0	Yes	47%
IB	T2	N0	M0		
IIA	T1	N1	M0	Yes	26%
IIB	T2	N1	M0		
	T3	N0	M0		
IIIA	T1	N2	M0	Potentially operable in some cases	
	T2	N2	M0		
	T3	N1	M0		8%
	T3	N2	M0		
IIIB	Any T	N3	M0	No	
	T4	Any N	M0		
IV	Any T	Any N	M1	No	2%

Stage I NSCLC represents a tumor that has not spread to the lymph nodes. The major difference between stage IA and IB disease is in the size of the primary tumor. Stage II NSCLC is characterized by a primary tumor that has spread to the hilar lymph nodes on the same side of the chest as the tumor. A tumor involving the chest wall without hilar node involvement is also considered stage II disease. Stage IIIA NSCLC includes tumors that have invaded the chest wall, diaphragm, the pleura of the mediastinum or heart, with hilar or mediastinal node involvement on the same side of the chest as the primary tumor. Stage IIIB disease includes any size tumor that has invaded any of the vital structures of the mediastinum, the carina, or the spine, with or without lymph node involvement.

A unique form of stage IIIB NSCLC involves a lung tumor and presence of tumor cells in the pleural fluid (malignant pleural effusion) but shows no evidence of metastatic disease. This is often referred to as wet IIIB disease, and is treated in the same way as stage IV NSCLC. Finally, the most advanced stage of NSCLC, stage IV disease, refers to the presence of distant metastases, i.e. the spread of the tumor beyond regional lymph nodes.

Goals of therapy

For patients who present with operable NSCLC (generally stage I–II disease) the goal of therapy is usually to eliminate the tumor completely (i.e. to achieve a cure). A cure is also achieved in 20–30% of patients with locally advanced (stage III) disease. For the remaining 70–80% of patients with locally advanced disease who are not cured, multimodality treatment may be prescribed with the aim of achieving as complete a response as possible.

Conversely, for the one in three patients who present with incurable, wet IIIB or stage IV NSCLC, the goals of therapy are palliative (i.e. to reduce tumor burden, relieve signs and symptoms, improve quality of life, and prolong survival). In addition, factors such as patient age and performance status

affect a patient's ability to tolerate treatment—older patients and those with poor performance status may be less able to tolerate aggressive therapy, which in turn affects treatment goals.

Evaluating response to therapy

Response to treatment and disease progression in NSCLC are usually determined using the Response Evaluation Criteria In Solid Tumours (RECIST). RECIST (Therasse et al. 2000) differs from the "older" World Health Organization (WHO) criteria in how tumor reduction is measured. The WHO criteria measure tumor reduction in two dimensions, whereas the RECIST criteria measure tumor reduction in one dimension, which makes tumor measurement easier and is as effective as bidimensional measurement for evaluating tumor responses.

Current therapy options

Despite recent advances in the treatment of NSCLC, only a small proportion of patients are diagnosed early enough to be cured with surgery or, in some cases, radiation therapy. Only ~30% of cases of NSCLC cases are diagnosed early enough to be cured by surgery (Carney & Hansen 2000) and only ~50% of patients who undergo surgical resection are still alive 5 years later (Evans 2004). Several treatment guidelines have been published (Detterbeck et al. 2003; Jett et al. 2003; Kvale et al. 2003; Mathur et al. 2003; Robinson et al. 2003; Scott et al. 2003; Smythe 2003; Socinski et al. 2003; Pfister et al. 2004). Treatment options depend upon the stage of disease (as discussed below).

Stage I–II NSCLC

For patients with stage I–II NSCLC, surgical resection is the treatment of choice. For patients with IA disease, surgery alone is usually sufficient to achieve a cure. For patients with operable stage IB or IIA disease, adjuvant chemotherapy and/or radiotherapy is often given with the aim of eliminating any residual disease left behind after surgery, thus reducing the risk of relapse (Evans 2004; Pathak et al. 2004). For patients diagnosed with stage I–II operable NSCLC the 5-year postsurgery survival rate is 60–80% (Naruke et al. 1988; Martini et al. 1992). A comprehensive review of surgery ± adjuvant therapy in patients with stage I–II NSCLC is beyond the scope of this article. However, the reader is referred to the guidelines referenced above.

Locally advanced stage III NSCLC

Surgery is sometimes an option for patients with stage IIIA and IIIB NSCLC. Patients with unresectable IIIA or IIIB NSCLC generally receive platinum-based chemotherapy, radiotherapy, or chemoradiotherapy, which is potentially curative in some cases (Dillman et al. 1990; Le Chevalier et al. 1991, 1992; Schaake-Koning et al. 1992; Sause 1995; Pathak et al. 2004). A complete review of the treatment of locally advanced NSCLC is beyond the scope of this article, and the reader is referred to the guidelines referenced above.

Wet IIIB and stage IV (metastatic) NSCLC

Platinum-based chemotherapy has for a long time been the mainstay of first-line therapy for patients with wet IIIB or stage IV NSCLC (Ramalingam & Belani 2004). A meta analysis conducted in 1995 demonstrated improved survival with cisplatin-based combination chemotherapy compared with older cytotoxic agents such as alkylating agents [hazard ratio (HR) 0.73 vs 1.26, respectively] (NSCLC Collaborative Group 1995). In 1990s "new cytotoxic" agents including docetaxel, paclitaxel, vinorelbine, gemcitabine, irinotecan, and tirapazamine were developed and were shown to have impressive single-agent activity in advanced, inoperable, wet IIIB/stage IV NSCLC. This led to exploring the use of cisplatin plus new cytotoxic combinations, which were shown to provide superior response rates and longer survival compared with cisplatin alone (Table 4). Further randomized trials demonstrated that doublet combinations consisting of a platinum agent plus a new cytotoxic were more efficacious than new cytotoxic monotherapy (Table 4). There are many potential combinations of platinum agent plus new cytotoxic. However, these platinum-based doublets are broadly comparable with regard to response rates and survival (Schiller et al. 2002).

In seeking to enhance the efficacy of doublet combinations, the use of triplet combinations (i.e. a platinum agent plus two new cytotoxic agents) was explored. However, the efficacy of triplets is not superior to that of doublets, and furthermore, triplet therapy is associated with greater toxicity compared with doublets (Alberola et al. 2001; Rudd et al. 2002). Consequently, a platinum agent plus a new cytotoxic doublets remain the first-line standard of care for patients with advanced, inoperable NSCLC.

Approximately 30–40% of patients with NSCLC are >70 years of age (Lee-Chiong & Matthay 1993) and concerns have been raised regarding the ability of these patients to tolerate platinum-based chemotherapy. However, for elderly patients with good performance status (PS), a platinum-based combination is the preferred treatment, whereas less toxic nonplatinum regimens may be more appropriate for patients with poor PS (Ramalingam & Belani 2004).

Second-line therapy

Single-agent docetaxel, pemetrexed, and erlotinib have each been approved for the second-line treatment of stage IIIB/IV NSCLC.

The approval of docetaxel was based on the outcomes of phase III trials conducted in patients with disease progression following platinum-based chemotherapy (Fossella et al. 2000; Shepherd et al. 2000). These studies demonstrated that, despite low response rates, second-line treatment with single-agent docetaxel provided modest improvements in quality of life and survival, compared with best supportive care, or treatment with either ifosfamide or vinorelbine.

Pemetrexed was approved following submission of the results of a large, phase III, randomized study comparing single-agent docetaxel with single-agent pemetrexed in the second-line treatment of patients with inoperable stage III/IV NSCLC (Hanna et al. 2004). This study demonstrated that pemetrexed provided clinically equivalent efficacy to docetaxel, but with a more favorable safety profile.

Erlotinib is a small molecule HER-1/EGFR inhibitor that blocks dysregulated EGFR-mediated intracellular signalling in NSCLC, inhibiting proliferation and permitting apoptosis of malignant cells. In a recent phase III study, treatment with erlotinib provided a significant survival advantage compared with placebo (median 6.7 vs 4.7 months, $P<0.001$) (Shepherd et al. 2004). In addition, patients treated with erlotinib experienced significant improvements in disease-related symptoms compared with placebo-treated patients, including prolonged time to deterioration of cough (28.1 vs 15.7 weeks, $P=0.04$), dyspnea (20.4 vs 12.1 weeks, $P=0.03$), and pain (12.1 vs 8.1 weeks, $P=0.04$).

Unmet needs

Surgery ± adjuvant chemotherapy/radiotherapy is potentially curative in patients who present with stage I–II and some cases of IIIA disease. Conversely, palliative, platinum-based chemotherapy continues to be the mainstay in the first-line treatment of inoperable, wet IIIB, and stage IV NSCLC, and while the development of the new cytotoxic agents has widened treatment options, a chemotherapy efficacy plateau appears to have been reached (Herbst & Sandler 2004; Ramalingam & Belani 2004). Consequently, the prognosis for patients with wet IIIB/stage IV NSCLC remains extremely poor.

New treatment strategies that combine different mechanisms of action are therefore urgently required to improve outcomes in patients with wet IIIB/stage IV NSCLC. A novel agent that is well tolerated in combination with chemotherapy and other agents active in NSCLC, and improves response rates, quality of life, and survival in this patient group would be a major therapeutic advance.

Angiogenesis: a rational target for therapy

In striving to develop novel, targeted anticancer treatment strategies, research has recently focused on the development of agents that inhibit tumor angiogenesis (i.e. inhibit the creation of new blood vessels to the tumor from preexisting vessels). The rationale underpinning this strategy is that antiangiogenic therapy limits the tumor's vascular supply, limiting tumor growth, and preventing tumor cells from reaching the systemic circulation and forming distant metastases (Folkman 1990). It therefore seems logical that the optimal use of antiangiogenic agents should be in combination with cytotoxic agents, providing a dual attack on the tumor itself and its vascular support system.

Once a tumor develops beyond 2 mm in diameter, the development of tumor vasculature is stimulated by the "angiogenic switch," an imbalance of proangiogenic and antiangiogenic factors (Brem et al. 1976, 1999; Carmeliet & Jain 2000; Herbst & Fidler 2000; Liekens et al. 2001; Carmeliet 2003).

Table 4	Randomized controlled trials comparing the efficacy of various platinum-based chemotherapy regimens in advanced NSCLC				
Treatment regimen	**Number of patients**	**Response rate (%)**	**Median survival (months)**	**1-year survival (%)**	**Reference**
Single platinum agent vs doublet therapy					
Cisplatin	522	11	7.6	28	Sandler et al. 2000
Cisplatin + gemcitabine		30	9.1	39	
Cisplatin	446	14	6.4	23	von Pawel et al. 2000
Cisplatin + tirpazamine		28	8.0	34	
Cisplatin	432	12	6.0	20	Wozniak et al. 1998
Cisplatin + vinorelbine		26	8.0	36	
High-dose cisplatin	414	17	8.6	36	Gatzemeier et al. 2000
Cisplatin + paclitaxel		26	8.1	30	
New cytotoxic agent alone vs platinum doublet combinations					
Paclitaxel	561	17	6.8	33	Lilenbaum et al. 2002
Paclitaxel + carboplatin		29	8.6	37	
Gemcitabine	334	12	9.0	32	Sederholm 2002
Gemcitabine + carboplatin		30	11.0	44	
Docetaxel	308	20	8.0	40	Georgoulias et al. 2001
Docetaxel + cisplatin		36	10.0	45	
Irinotecan	259	21	11.0	44	Masuda et al.1999
Irinotecan + cisplatin		43	12.0	49	
Comparisons of various platinum doublet combinations					
Cisplatin + vinorelbine		25	10.1	41	
Cisplatin + docetaxel	1218	32	11.3	46	Rodriguez et al. 2001
Carboplatin + docetaxel		24	9.1	38	
Cisplatin + paclitaxel		21	7.8	31	
Cisplatin + gemcitabine	1105	21	8.1	36	Schiller et al. 2002
Cisplatin + docetaxel		17	7.4	31	
Carboplatin + paclitaxel		15	8.2	35	
Cisplatin + vinorelbine	408	28	8.0	36	Kelly et al. 2001
Cisplatin + paclitaxel		25	8.0	38	
Cisplatin + etoposide	369	14	7.5	37	Belani et al. 1998
Carboplatin + paclitaxel		22	6.3	32	
Cisplatin + vindesine	199	22	10.0	41	Niho et al. 1999
Cisplatin + irinitocan		29	10.0	36	
NSCLC, nonsmall cell lung cancer.					

The proangiogenic molecule, VEGF, is central to the activation of the angiogenic switch (Senger et al. 1983; Ferrara et al. 2003; Hicklin & Ellis 2005) (Fig. 2). The expression of this key molecule is stimulated by a number of factors in the tumor microenvironment, including hypoxia, cytokine release, mechanical stress, and upregulation of oncogenes. The production of VEGF by the tumor creates a positive feedback loop by which VEGF-induced angiogenesis allows more tumor growth. As a result of its rapid growth, the tumor outstrips its blood supply and the supply of oxygen and nutrients becomes inadequate, resulting in areas of relative hypoxia. Hypoxia stimulates further VEGF production, which in turn stimulates further vessel formation, and once the tumor has entered this vascular phase, new vessels continue to form for as long as the tumor continues to grow. In addition, VEGF increases the permeability of the tumor vasculature to circulating macromolecules, allowing plasma proteins to leak, resulting in the formation of proangiogenic stroma. A further consequence of this increased vascular permeability is that tumor interstitial pressure is increased, reversing normal pressure gradients within tissues and ultimately impeding the delivery of chemotherapeutic agents. VEGF-driven angiogenesis also promotes the contact between blood vessels and tumor cells, offering a route for tumor cells to invade those vessels and form distant metastases. Furthermore, excessive VEGF production results in the formation of vessels that are immature and hyperpermeable, which facilitates this invasion. VEGF is also involved in lymphangiogeneisis: the formation of giant lymphatic vessels, thus providing another potential route by which the tumor can metastasize (Fig. 2).

The role of angiogenesis in NSCLC progression is well established: high microvessel density is a strong prognostic factor for metastasis and poor survival (Fontanini et al. 1995; D'Amico et al. 1999; Cox et al. 2000; O'Byrne et al. 2000; Yano et al. 2000; Meert et al. 2002). In addition, molecular studies have confirmed that VEGF mRNA is upregulated in lung tumors (Toi et al. 2001). In NSCLC specimens a positive correlation has been demonstrated between upregulated VEGF expression, high tumoral microvessel density, and poor prognosis (Volm et al.1997;

Imoto et al. 1998; Koukourakis et al. 2000; O'Byrne et al. 2000; Ushijima et al. 2001; Yuan et al. 2001). Inhibition of VEGF signalling is therefore an attractive and rational therapeutic strategy in NSCLC (Ferrara 2004; Herbst & Sandler 2004). Anti-VEGF therapy has the potential to restrict tumor growth and metastasis by inhibiting angiogenesis and lymphangiogenesis, and the potential to improve the delivery of concomitant cytotoxic therapy by reducing tumor interstitial pressure (Herbst & Sandler 2004) (Fig. 2).

The anti-VEGF, antiangiogenic approaches that have received most attention to date include:

- inhibiting VEGF itself using neutralizing anti-VEGF monoclonal antibodies or soluble receptors

- VEGF receptor (VEGFR) blockade using anti-VEGFR monoclonal antibodies

- inhibiting VEGFR signalling with small molecule VEGFR tyrosine kinase inhibitors.

Clinical evidence for bevacizumab in NSCLC

Bevacizumab is a recombinant, humanized, anti-VEGF, monoclonal antibody that exerts a direct antiangiogenic effect by binding to and clearing VEGF from the tumor microenvironment (reviewed by Presta et al. 1997; Salgaller 2003; Herbst & Sandler 2004; Kerr 2004; Sandler at al. 2004a; Adams & Weiner 2005; Culy 2005; Midgley & Kerr 2005; Rhee & Hoff 2005). In a murine xenograft model of human NSCLC, bevacizumab was shown to inhibit tumor growth (Kabbinavar et al. 1995). In addition, in accord with the current thinking that hypoxia-induced production of VEGF mediates tumoral resistance to radiotherapy and chemotherapy (Harmey & Bouchier-Heyes 2002), the anti-VEGF activity of bevacizumab has been shown to augment the responsiveness of NSCLC tumors to radiotherapy and platinum-based chemotherapy in nude mice (Kabbinavar et al. 1995). *In-vitro* studies have demonstrated synergistic efficacy of
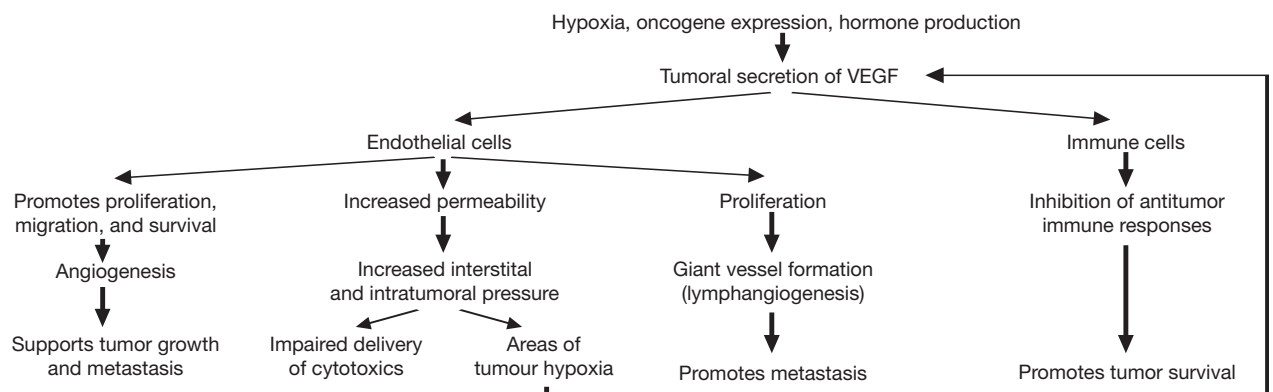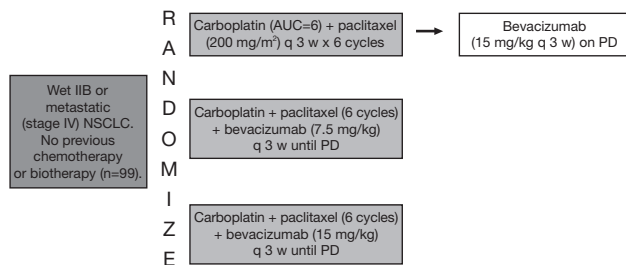

Fig. 2 | Role of vascular endothelial growth factor (VEGF) in tumor growth. NSCLC, nonsmall cell lung cancer

a | Phase II trial of carboplatin/paclitaxel ± high- or low-dose bevacizumab in patients with wet IIIB/stage IV NSCLC (Johnson et al. 2004)

b | Phase II/III randomized trial of carboplatin/paclitaxel plus bevacizumab in patients with previously untreated, wet IIIB/stage IV, nonsquamous NSCLC (Tyagi 2005; Sandler et al. 2005a,b)
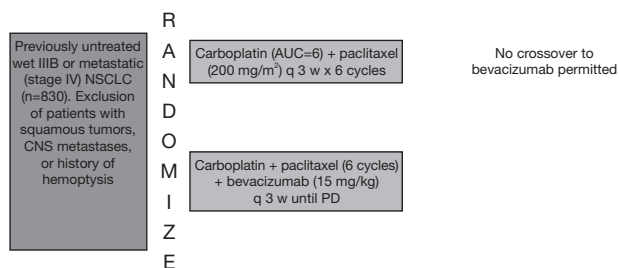
c | Phase I/II single-arm trial of bevacizumab and erlotinib in patients with wet IIIB/stage IV nonsquamous NSCLC who have relapsed following platinum-based chemotherapy (Herbst et al. 2005)

Phase I	Phase II
Group 1 (n=3) Erlotinib (100 mg/day, p.o.) Bevacizumab (7.5 mg/kg, i.v.)	
Group 1 (n=3) Erlotinib (100 mg/day, p.o.) Bevacizumab (15 mg/kg, i.v.)	
Group 1 (n=3) Erlotinib (150 mg/day, p.o.) Bevacizumab (15 mg/kg, i.v.) →	Additional 28 patients recruited at the group 3 dose

Fig. 3 | Study designs investigating bevacizumab in patients with NSCLC. AUC, area under the curve; CNS, central nervous system; i.v., intravenous; NSCLC, nonsmall cell lung cancer; PD, progressive disease; q 3 w, every 3 weeks

bevacizumab and docetaxel in endothelial cells (Sweeney et al. 2001), and bevacizumab also appears to reverse VEGF-mediated inhibition of dendritic cell differentiation, resulting in enhanced antitumor immune responses (Gabrilovich et al. 1998, 1999).

Three clinical studies investigating bevacizumab in the treatment of NSCLC have been published to date:

- A phase II, randomized study comparing carboplatin, paclitaxel, and bevacizumab (7.5 mg/kg or 15 mg/kg) with carboplatin and paclitaxel alone in 99 patients with wet IIIB (n=15) or stage IV NSCLC (n=84) who had received no previous chemotherapy or biotherapy (Johnson et al. 2004; Figure 3a). The carboplatin/paclitaxel doublet was selected for use in combination with bevacizumab for three reasons:

  – Carboplatin/paclitaxel is generally less toxic than other platinum doublets (Schiller et al. 2002)

  – When combined with antiangiogenic therapy, the antitumor activity of carboplatin/paclitaxel is enhanced in animal models of NSCLC and breast cancer (Herbst et al. 1998)

  – Carboplatin/paclitaxel and bevacizumab combined was well tolerated in a phase I study conducted in patients with various types of advanced cancers (Margolin et al. 2001).

- A phase II/III, randomized study comparing carboplatin, paclitaxel, and bevacizumab (15 mg/kg) with carboplatin and paclitaxel alone in 878 previously untreated patients with wet IIIB or stage IV NSCLC (excluding NSCLC categorized as squamous cell carcinoma and patients who have previously experienced hemoptysis) (Tyagi 2005; Sandler et al. 2005a,b, 2006; Dowlati et al. 2006; Figure 3b).

- A phase I/II, single-arm study of bevacizumab and erlotinib combined in 40 patients with wet IIIB or stage IV NSCLC (excluding NSCLC characterized as squamous cell carcinoma) who had relapsed after at least one platinum-based regimen (Herbst et al. 2003, 2004, 2005; Mininberg et al. 2003; Sandler et al. 2003, 2004b; Tsao et al. 2005; Figure 3c). Erlotinib was selected as a combination drug with bevacizumab for the following reasons:

  – Erlotinib has shown impressive single agent activity in recurrent stage III/IV NSCLC (Perez-Soler et al. 2004)

  – Bevacizumab and erlotinib have demonstrated synergistic activity in human colon cancer xenograft models (Herbst et al. 2003)

  – Other HER-1/EGFR and VEGF dual blockade strategies have demonstrated impressive antitumor activity in human tumor xenograft models (e.g. cetuximab, an anti-HER-1/EGFR monoclonal antibody, combined with either DC101, an anti-VEGFR monoclonal antibody, or VEGF-antisense technology) (Ciardiello et al. 2000; Shaheen et al. 2001; Jung et al. 2002).

Table 5 | Efficacy of bevacizumab combinations in stage IIIB/stage IV NSCLC

Study	Patient group	Treatment	Outcome		
			ORR (%)	Median PFS or TTP	Median OS
Phase II (Johnson et al. 2004)	Stage IIIB/IV NSCLC of all histologic subtypes, no previous chemotherapy or biotherapy (n=99)	C + P	18.8	4.2 (TTP)	14.9[a]
		C + P + Bev (7.5 mg/kg)	28.1	4.3 (TTP)	11.6[b]
		C + P + Bev (15 mg/kg)	31.5	7.4[c] (TTP)	17.7
Phase II/III (Sandler et al. 2005a,b)	Previously untreated stage IIIBIV nonsquamous NSCLC (n=878)	C + P	10	4.5 (PFS)	10.2
		C + P + Bev (15 mg/kg)	27[c]	6.4[c] (PFS)	12.5[c]
Phase I/II (Herbst et al. 2005)	Recurrent stage IIIB/IV nonsquamous NSCLC (relapsed after at least one platinum-based regimen) (n=40)	Bev (15 mg/kg) + Erl	20	7.0 (PFS)	12.6

[a]Patients the C + P (control group) were allowed to cross over to treatment with bevacizumab (15 mg/kg) upon disease progression, which may explain why median survival was longer than expected in this treatment group.

[b]The majority of patients with squamous cell NSCLC were in the low-dose bevacizumab group, accounting in part for the lower survival compared with the high-dose bevacizumab group.

[c]Denotes significant improvement compared with C + P alone.

Bev, bevacizumab; C, carboplatin; Erl, erlotinib; NSCLC, nonsmall cell lung cancer; ORR, overall response rate; OS, overall survival; P, paclitaxel; PFS, progression-free survival; TTP, time to progression.

Outcomes from these three studies are reviewed in the following sections, and efficacy endpoints are summarized in Table 5.

In addition, there is limited evidence, only available in abstract form at the time of writing, of preliminary results with bevacizumab: plus gemcitabine and carboplatin (Kraut 2006); plus gemcitabine and oxaliplatin (Davila et al. 2006); and plus pemetrexed and carboplatin (Patel et al. 2006).

Response rates

Bevacizumab combined with carboplatin/paclitaxel

In the phase II trial of carboplatin/paclitaxel ± bevacizumab in previously untreated patients with wet IIIB or stage IV NSCLC, antitumor efficacy appeared to be greatest with high-dose bevacizumab, compared with low-dose bevacizumab (Johnson et al. 2004; Table 6). However, the study was not sufficiently powered to demonstrate a definitive dose–response relationship. When responses were evaluated by the study investigators, the overall response rate (ORR) with carboplatin/paclitaxel plus high-dose bevacizumab was 31.5%, compared with 18.8% in patients treated with carboplatin/paclitaxel alone.

When responses were evaluated by an independent review facility (IRF), the ORR in the high-dose bevacizumab group was 40.0%, compared with 31.3% in patients treated with carboplatin/paclitaxel alone.

In addition, of 19 patients in the carboplatin/paclitaxel group who switched to bevacizumab monotherapy on disease progression, five achieved stable disease that was maintained for >6 months.

In the subsequent phase II/III study (Sandler et al. 2005a,b; Tyagi 2005), which excluded patients with tumors categorized as predominantly of the squamous cell subtype (see Safety and tolerability section below), the first interim analysis confirmed that the addition of bevacizumab to carboplatin/paclitaxel chemotherapy produced significantly higher response rates compared with carboplatin/paclitaxel chemotherapy alone (ORR 27.2 vs 10.0%, P<0.0001; partial response rate: 25.8 vs 10%; complete response rate: 1.4 vs 0%).

Bevacizumab combined with erlotinib

In the phase I/II study of bevacizumab plus erlotinib conducted in patients with wet IIIB and stage IV NSCLC who had relapsed

Table 6 | Phase II efficacy of carboplatin and paclitaxel ± bevacizumab in patients with wet IIIB/stage IV NSCLC (Johnson et al. 2004)

	C + P (controls) (n=32)		C + P + Bev (7.5 mg/kg) (n=32)		C + P + Bev (15 mg/kg) (n=34)	
	All patients	Nonsquamous	All patients	Nonsquamous	All patients	Nonsquamous
ORR (%)	18.8	20	28.1	31.8	31.5	50
Median TTP (months)	4.2	4.0	4.3	6.3	7.4	7.1
Median OS (months)	14.9	12.2	11.6	14.0	17.7	17.8

Responses shown are investigator responses.

Bev, bevacizumab; C, carboplatin; NSCLC, nonsmall cell lung cancer; ORR, overall response rate; OS, overall survival; P, paclitaxel; PFS, progression-free survival; TTP, time to progression.

following platinum-based therapy (Herbst et al. 2005), the disease control rate (all patients achieving at least stable disease) for the entire study population (i.e. phase I and phase II combined, n=40) was 85%. Eight patients (20%) achieved partial responses, 26 patients (65%) achieved stable disease, and only six patients (15%) developed progressive disease.

All eight responders had adenocarcinomas. However, 30/40 patients enrolled onto this study had adenocarcinomas (patients with tumors classified as squamous cell carcinomas were excluded to minimize bleeding risk), making it impossible to ascertain whether patients with adenocarcinoma are more likely to respond to treatment with bevacizumab plus erlotinib than patients with other NSCLC histologic subtypes.

Bevacizumab in other combinations

Preliminary results show partial responses in seven (31%) and stable disease in eight (36%) of 22 evaluable patients receiving bevacizumab in combination with gemcitabine 1000 mg/m^2 plus oxaliplatin 130 mg/m^2 (Davila et al. 2006), and a partial and a minor response in one patient each from six receiving the drug in combination with pemetrexed 500 mg/m^2 plus carboplatin (Patel et al. 2006).

Time to progression/progression-free survival

Bevacizumab combined with carboplatin/paclitaxel

In the phase II study (Johnson et al. 2004), the addition of high-dose bevacizumab to carboplatin/paclitaxel chemotherapy significantly prolonged time to progression compared with carboplatin/paclitaxel chemotherapy alone (7.4 vs 4.2 months, respectively; P=0.023, based on investigators' own assessment of disease progression). This represents a 46% reduction in the risk of disease progression (Cox proportional hazard model). When disease progression was assessed by the IRF the addition of high-dose bevacizumab to carboplatin/paclitaxel chemotherapy was shown to prolong time to progression compared with carboplatin/paclitaxel alone, although this difference failed to reach statistical significance (7.0 vs 5.9 months).

The subsequent phase II/III trial (Sandler et al. 2005a,b; Tyagi 2005) confirmed that the addition of bevacizumab to carboplatin/paclitaxel chemotherapy resulted in significantly prolonged median progression-free survival (PFS), compared with carboplatin/paclitaxel chemotherapy alone (6.4 vs 4.5 months, P<0.0001).

Bevacizumab combined with erlotinib

In the phase I/II study of bevacizumab plus erlotinib (Herbst et al. 2005), 1-year PFS was 38.0% (95% CI 24.3%, 59.6%), and median PFS was 7.0 months. These results were very encouraging considering that this was a cohort of extremely poor prognosis patients with wet IIIB/stage IV NSCLC (classified as a nonsquamous NSCLC) who had relapsed after receiving platinum-based chemotherapy.

Overall survival

Bevacizumab combined with carboplatin/paclitaxel

In the phase II study, addition of high-dose bevacizumab (15 mg/kg) to first-line carboplatin/paclitaxel chemotherapy resulted in a modest increase in overall survival compared with chemotherapy alone (17.7 vs 14.9 months) (Johnson et al. 2004). However, overall survival in the chemotherapy alone group was strikingly high (14.9 months) compared with median survival reported in cooperative phase III trials of carboplatin/paclitaxel in similar patient cohorts (~8 months). This is possibly due to 19/32 patients in the carboplatin/paclitaxel group crossing over to treatment with high-dose bevacizumab on disease progression (after crossover 1-year survival in these 19 patients was 47.4%).

The first interim analysis of data from the subsequent phase II/III trial (Tyagi 2005) confirmed that median survival in patients treated with carboplatin/paclitaxel plus bevacizumab followed by bevacizumab monotherapy until disease progression was significantly longer than in patients who received carboplatin/paclitaxel alone (HR 0.77; 12.5 vs 10.2 months; P=0.007). Exploratory subgroup analyses demonstrated that the addition of bevacizumab to chemotherapy provided survival benefit irrespective of tumor stage, weight loss, previous radiotherapy, race, performance status, and age. However, while survival was significantly improved in males treated with carboplatin/paclitaxel plus bevacizumab compared with carboplatin/paclitaxel alone (HR 0.69, P=0.003), the survival advantage achieved with bevacizumab in females failed to reach statistical significance (HR 0.96, P=0.80). Explanations for this apparent survival difference by gender include possible imbalances in unmeasured baseline prognostic factors (e.g. smoking history was not collected in this study), differences between males and females in the use of subsequent second- and third-line therapy (only details of second-line therapy were collected), chance alone, or may indeed may reflect a true gender difference regarding the survival benefits offered by bevacizumab.

Bevacizumab combined with erlotinib

In the phase I/II study of bevacizumab plus erlotinib (Herbst et al. 2005), median overall survival was 12.6 months, and the 1-year survival rate was 54.2% (95% CI 40.0%, 73.4%). Further studies are now needed to confirm these encouraging data in larger patient cohorts.

Prognostic factors

Identifying prognostic factors will assist in the selection of patients with NSCLC who are most likely to respond well to treatment with bevacizumab, thus facilitating individualized patient care. Potential prognostic factors that are currently under investigation in the ongoing phase II/III study of carboplatin/paclitaxel ± bevacizumab in patients with previously untreated wet IIIB and stage IV NSCLC (other than the squamous cell subtype) include the following: serum VEGF, soluble E selectin, soluble intracellular adhesion molecule-1 (ICAM), and

basic fibroblast growth factor (bFGF) levels (Sandler et al. 2005a,b), all of which are markers for angiogenic activity. Low baseline ICAM levels were predictive of improvements in PFS with bevacizumab (Dowlati et al. 2006).

In the phase I/II study of bevacizumab plus erlotinib in patients with relapsed wet IIIB/stage IV nonsquamous NSCLC, pretreatment serum samples were analyzed by mass spectrometery, resulting in the identification of protein/peptide expression patterns that discriminated between responders and those who experienced disease progression (Salmon et al. 2005). Additional work is planned to validate these preliminary data and to identify which specific plasma proteins have prognostic value.

Quality of life

Of interest, there are currently no available data on quality of life benefits in patients with NSCLC treated with bevacizumab, and in the palliative setting, quality of life benefits are likely to be just as important to patients as prolongation of survival.

Safety and tolerability

The safety and tolerability profile of bevacizumab has been extensively investigated in NSCLC and the majority of reported adverse events have been noted to be either manageable or not clinically relevant. However, some safety concerns have been raised, particularly regarding potentially life-threatening bleeding events. Moreover, reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in clinical studies with bevacizumab. RPLS involves leaking from brain capillaries and is associated with hypertension, fluid retention, and the cytotoxic effects of immunosuppressive drugs on the vascular endothelium. Symptoms include headache, seizures, lethargy, confusion, and visual disturbances. Although occurring in fewer than 0.1% of patients, it is considered sufficiently serious to warrant a warning on the prescribing information in September 2006 (Anon. 2006).

Impact on chemotherapy-related toxicity

If bevacizumab is to be successfully incorporated into existing chemotherapy regimens in NSCLC it is important that it does not exacerbate chemotherapy-related toxicities. Experience to date with bevacizumab in patients with NSCLC has shown that combining bevacizumab with carboplatin/paclitaxel does not increase the incidence or severity of nausea, vomiting, renal toxicity, or neuropathy, which are typically associated with chemotherapy. However, the addition of bevacizumab to carboplatin/paclitaxel chemotherapy is associated with an apparent dose-dependent increased risk of leukopenia/neutropenia, and a slight increase in the incidence of diarrhea and minor systemic events, including fever, headache, rash, and chills (Johnson et al. 2004).

Bleeding events

In the phase II study of carboplatin/paclitaxel ± bevacizumab (Johnson et al. 2004), two distinct patterns of bleeding were observed: minor mucocutaneous hemorrhage, and severe and sometimes fatal bleeding (hemoptysis or hematemesis). The most common mucocutaneous bleeding was National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 1–2 epistaxis, which was reported in 31% of patients treated with low-dose bevacizumab, and 44% of patients treated with high-dose bevacizumab, compared with only 6% of patients treated with chemotherapy alone. None of these minor bleeding events required a change in bevacizumab administration. Of greater concern, six patients treated with bevacizumab experienced life-threatening bleeding, which was fatal in four patients. These life-threatening bleeding events were more frequent in the low-dose bevacizumab group (5/6 cases) than the high-dose bevacizumab group (1/6 cases), occurred both early (≤60 days) and late (≥180 days) in treatment, and were more frequent in patients with NSCLC classified as squamous cell carcinomas (4/13 patients) than patients with adenocarcinomas (2/54 patients). Consequently, patients with squamous cell NSCLC were excluded in subsequent studies of bevacizumab in NSCLC (Johnson et al. 2004).

In the subsequent phase II/III trial of carboplatin/paclitaxel ± bevacizumab which excluded patients with squamous cell histology (Sandler et al. 2005a,b), the incidence of severe (≥grade 3) hemoptysis was 1.9% (8/420) in the carboplatin/paclitaxel plus bevacizumab group versus 0.2% (1/427) in the chemotherapy alone group ($P<0.04$). Of 420 patients who were treated with bevacizumab, seven died as a result of bleeding events (five cases of hemoptysis, two cases of GI bleeding), compared with 1/427 patients who were treated with chemotherapy alone. However, this study indicates that the exclusion of patients with predominantly squamous cell disease drastically reduces the risk of severe and fatal pulmonary hemorrhage. A retrospective analysis of the patients in this study revealed ten cases of pulmonary hemorrhage in 425 patients who received bevacizumab, six of which occurred within 150 days of beginning treatment, and no evidence of clinical risk factors at baseline (Sandler et al. 2006).

In the phase I/II trial of bevacizumab and erlotinib combined, which also excluded patients with squamous cell histology (Herbst et al. 2005), only 6% of patients receiving bevacizumab 15 mg/kg developed mild epistaxis, and importantly there were no life-threatening bleeding events.

Proteinuria

Treatment with bevacizumab in patients with NSCLC is associated with an increased incidence of proteinuria. In the phase II trial of carboplatin/paclitaxel ± bevacizumab (Johnson et al. 2004) 7/32 patients in the low-dose bevacizumab group and 14/32 patients in the high-dose bevacizumab group developed asymptomatic proteinuria, compared with 2/32 patients in the chemotherapy alone group. Similarly, in the phase I/II trial of bevacizumab combined with erlotinib (Herbst et al. 2005), 9% of patients who received the phase II dose of bevacizumab (15 mg/kg) developed proteinuria.

Hypertension

As reported in trials in other solid tumor indications, treatment with bevacizumab in patients with NSCLC appears to be associated with an increased risk of hypertension. In the phase II study of carboplatin/paclitaxel ± bevacizumab (Johnson et al. 2005), 5/32 patients treated with high-dose bevacizumab and 6/34 patients treated with low-dose bevacizumab developed hypertension, compared with only 1/32 patients treated with chemotherapy alone. Of those patients who developed hypertension, the greatest increases in systolic blood pressure were observed in patients who received high-dose bevacizumab. However, no patient on this phase II study discontinued treatment due to hypertension.

In the subsequent phase II/III study (Sandler et al. 2005a,b; Tyagi 2005), the incidence of grade 3 hypertension was significantly higher in patients treated with carboplatin/paclitaxel plus bevacizumab, compared with those who were treated with chemotherapy alone (6 vs 0.7%, $P{\leq}0.001$), and in the phase I/II study of bevacizumab plus erlotinib (Herbst et al. 2005), a similar proportion of patients (2/40) developed grade 3–4 hypertension.

Although treatment with bevacizumab is associated with hypertension, it can be effectively managed with oral antihypertension medications such as angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers. In addition, data from a study investigating long-term treatment with bevacizumab in patients with a range of different solid tumors suggest that bevacizumab-related hypertension decreases with long-term use (Langmuir et al. 2002).

Thrombotic events

In the phase II study of carboplatin/paclitaxel ± bevacizumab (Johnson et al. 2004) there was a slight increase in the frequency of thrombotic events in patients who were treated with low- and high-dose bevacizumab, compared with those who received chemotherapy alone (9.4% in the chemotherapy alone group, 12.5% in the low-dose bevacizumab group, 17.6% in the high-dose bevacizumab group). However, in the subsequent phase II/III study conducted in patients with nonsquamous NSCLC (Sandler et al. 2005a,b), no significant increase in the frequency of grade $\geq$3 arterial thrombosis or grade $\geq$3 venous thrombosis was observed in patients treated with carboplatin/paclitaxel plus bevacizumab, compared with those who received chemotherapy alone (arterial thrombosis 1.9 vs 1.0%; venous thrombosis 3.8 vs 3.0%). Moreover, no thrombotic events were recorded in the phase I/II study of bevacizumab plus erlotinib in 40 patients with relapsed nonsquamous NSCLC (Herbst et al. 2005). However, in a pooled analysis of data from five randomized trials involving patients with metastatic breast cancer, colorectal cancer, and NSCLC, bevacizumab and chemotherapy combined was associated with a significantly higher incidence of arterial thrombotic events compared with chemotherapy alone (3.8 vs 1.7%, $P<0.01$), especially in patients $\geq$65 years old with a prior history of thromboembolic events (Skillings et al. 2005).

Ongoing clinical development

The results of the first interim analysis of the phase II/III trial demonstrating significantly prolonged survival in patients treated with carboplatin/paclitaxel plus bevacizumab compared with chemotherapy alone has prompted the initiation of a range of phase II and phase III studies investigating the potential for bevacizumab in combination with other platinum-based doublets in the first-line treatment of wet IIIB/stage IV NSCLC (Treat 2005). The doublets under investigation include: carboplatin/gemcitabine, cisplatin/gemcitabine, oxaliplatin/gemcitabine, and carboplatin/pemetrexed (Table 7). The potential for bevacizumab in combination with single-agent chemotherapy (docetaxel or pemetrexed) in the second-line treatment of advanced stage IIIB/IV NSCLC is also being explored (Table 7).

Based on the encouraging data from the phase I/II single-arm study of bevacizumab plus erlotinib (Herbst et al. 2005), three more studies are underway to further evaluate the clinical potential of this combination in the second-line treatment of stage IIIB/IV NSCLC:

Table 7	Planned and ongoing studies with bevacizumab for the treatment of stage IIIB/IV NSCLC	
Study design	**Inclusion criteria**
Phase II	
Single-arm study of carboplatin, gemcitabine, and bevacizumab in advanced NSCLC	Stage IIIB/IV NSCLC, newly diagnosed or recurrent after previous surgery and/or radiotherapy
Single-arm study of oxaliplatin, gemcitabine, and bevacizumab in the first-line treatment of advanced NSCLC	Previously untreated stage IIIB/IV NSCLC, excluding patients with squamous cell histology
Randomized study comparing bevacizumab + chemotherapy (docetaxel or pemetrexed) vs bevacizumab + erlotinib vs chemotherapy alone in patients with previously treated advanced NSCLC	Stage IIIB/IV, recurrent NSCLC with progression after previous platinum-based chemotherapy or adjuvant chemotherapy
Single-arm study of carboplatin, pemetrexed, and bevacizumab in patients with NSCLC	Stage IIIB, stage IV, or recurrent NSCLC, no prior systemic chemotherapy, exclusion of patients with squamous cell histology
Phase III	
Randomized study of cisplatin and gemcitabine ± bevacizumab (7.5 mg/kg or 15 mg/kg) in advanced NSCLC (AVAiL)	Stage IIIB/IV NSCLC, newly diagnosed or recurrent after previous surgery and/or radiotherapy
Randomized, placebo-controlled study of bevacizumab + erlotinib vs erlotinib alone in the second-line treatment of advanced NSCLC	Radiographic progression during or after first-line chemotherapy for stage IIIB/IV NSCLC
Randomized, placebo-controlled study of platinum-based chemotherapy combined with bevacizumab followed by bevacizumab + erlotinib vs bevacizumab + erlotinib placebo in the first-line treatment of advanced NSCLC	Stage IIIB, stage IV, or recurrent NSCLC, no prior systemic chemotherapy, exclusion of patients with squamous cell histology

- A phase III, randomized, double-blind, placebo-controlled study investigating the safety and efficacy of bevacizumab combined with platinum-based chemotherapy doublets followed by treatment with either bevacizumab plus erlotinib or bevacizumab plus placebo to disease progression in the first-line treatment of patients with stage IIIB/IV NSCLC (other than the squamous cell subtype)

- A phase III randomized, double-blind, placebo-controlled study comparing the safety and efficacy of bevacizumab plus erlotinib compared with erlotinib plus placebo in the second-line treatment of patients with stage IIIB/IV nonsquamous NSCLC following failure of first-line chemotherapy. This study will also investigate any potential pharmacokinetic interactions between these agents

- A phase II randomized trial comparing the safety and efficacy of bevacizumab plus erlotinib versus bevacizumab plus chemotherapy (docetaxel or pemetrexed) versus chemotherapy alone (docetaxel or pemetrexed) in the treatment of relapsed or refractory nonsquamous NSCLC

Economic evidence

The economic burden of NSCLC is huge. Not only are the direct costs of surgical resections, radiotherapy, and drug therapy high, the secondary costs associated with hospitalization, postoperative care, and management of adverse effects of chemotherapy are considerable. In addition, there are the societal costs associated with the impaired ability to work. Pharmacoeconomic data are readily available comparing the cost effectiveness of various different chemotherapy regimens in different patient subgroups (e.g. Clegg et al. 2001; Saglam et al. 2002; Szczepura 2002; Holmes et al. 2004; Neymark et al. 2005). Some preliminary pharmacoeconomic data regarding the use of bevacizumab in the treatment of NSCLC are available in abstract form.

Using the results of Sandler et al. (2005a,b), the incremental cost effectiveness of adding bevacizumab to carboplatin plus paclitaxel was calculated, based on Medicare reimbursement cost for January 2005 (Grusenmeyer & Gralla 2006). With a median overall survival increase of 2.3 months, the cost per life-year gained with bevacizumab was $US345 762. Reimbursement of bevacizumab would need to be $US14.70/10 mg to reach a threshold of $US100 000 per year of life gained, 74% lower than the 2005 Medicare value of $US57.08/10 mg.

Another study from the direct payer perspective using 2005 Canadian wholesale prices demonstrated a cost of $Can47 250 per patient with metastatic lung cancer for bevacizumab relative to conventional therapy (Drucker et al. 2006). The total lifetime cost to the Canadian healthcare system was estimated to be $Can262 million if bevacizumab was used for lung, breast, and colorectal cancer.

These preliminary results clearly reflect the drug acquisition cost for bevacizumab, reflecting the high cost of monoclonal antibody production.

Patient group/population

Patients with advanced, inoperable, stage IIIB/IV NSCLC

Previously untreated patients

For patients with wet IIIB/stage IV NSCLC, first-line treatment with a platinum-based chemotherapy agent (carboplatin or cisplatin) plus a new cytotoxic agent (e.g. docetaxel, paclitaxel, gemcitabine, or vinorelbine) has been the accepted standard of care in most countries. The phase II/III, randomized trial investigating the use of carboplatin/paclitaxel ± bevacizumab in patients with nonsquamous NSCLC is the first study to demonstrate a statistically significant survival advantage with a targeted agent plus chemotherapy versus chemotherapy alone. Consequently, bevacizumab combined with carboplatin/ paclitaxel is now the new Eastern Cooperative Oncology Group (ECOG) reference standard for the treatment of patients with previously untreated wet IIIB/stage IV nonsquamous NSCLC (Tyagi 2005). However, the safety of bevacizumab in combination with other chemotherapy combinations remains to be explored.

Patients with relapsed disease

For patients with wet IIIB/stage IV, nonsquamous NSCLC who have relapsed following first-line treatment with platinum-based chemotherapy, preliminary phase I/II data indicate that the combination of bevacizumab with the HER-1/EGFR inhibitor erlotinib was well tolerated, resulting in encouraging responses (Herbst et al. 2005). Previous studies have suggested that HER-1/EGFR inhibitors provide the greatest efficacy in females and patients who have never smoked. However, in this study the response rates were similar in males and females (26.3 and 14.3%, respectively), and in current/previous smokers versus life-long nonsmokers (19.4 vs 22.2%), suggesting that bevacizumab in combination with erlotinib is effective in a wider patient population than erlotinib alone. However, these preliminary data should be interpreted with caution due to the low number of patients (n=40) involved.

Patient selection to minimize pulmonary bleeding risk

The phase II study of carboplatin/paclitaxel ± bevacizumab (Johnson et al. 2004) demonstrated that patients with NSCLC classified as the squamous cell subtype (tumors of mixed histologies were classified by the predominant cell type) may not be suitable candidates for treatment with bevacizumab because they are at increased risk of experiencing serious, potentially life-threatening bleeding. In clinical practice, rigorous patient selection procedures will be extremely important in minimizing bleeding risk. Patients with NSCLC who should not receive bevacizumab because they are at increased risk of experiencing serious bleeding events include those with squamous cell carcinomas, brain metastases, a prior history of gross hemoptysis events, and patients receiving anticoagulants.

Patients with earlier-stage NSCLC

The encouraging efficacy of bevacizumab combined with either platinum-based chemotherapy or erlotinib demonstrated in

patients with wet IIIB/stage IV NSCLC justifies exploring the wider use of bevacizumab in patients with earlier-stage, operable NSCLC (Belani & Ramalingam 2005; Kerr 2005; Kris 2005; Martins 2005; Tyagi 2005). This includes using bevacizumab in both the neoadjuvant setting (i.e. in combination with chemotherapy or radiotherapy to reduce the tumor before surgery), and the adjuvant setting (after surgery) to treat residual disease.

There is a strong rationale for using bevacizumab in the adjuvant setting. Following surgical resection of the primary tumor, metastases can be present yet undetectable, ultimately leading to relapse. As these metastases are dependent on VEGF for the angiogenic switch to malignant growth, adjuvant treatment with bevacizumab could, in concept, reduce the risk of relapse. In addition, adjuvant chemotherapy is associated with significant toxicity, which can be unacceptable to patients who have undergone surgery and are potentially disease-free. For these patients, postoperative bevacizumab maintenance therapy is likely to be a better tolerated and therefore perhaps more attractive therapeutic option.

As already discussed, patients with NSCLC tumors classified as having predominant squamous cell histology should not be treated with bevacizumab-containing regimens because of the unacceptably high risk of serious pulmonary hemorrhage. However, in the postoperative (adjuvant) setting, the use of bevacizumab could potentially be extended to patients with both squamous and nonsquamous NSCLC for treating minimal residual disease (MRD) following neoadjuvant chemotherapy and surgical resection (Kris 2005). This is because hemoptysis is thought to be a consequence of bevacizumab-induced tumor disintegration and therefore once the tumor has been almost completely eliminated, even patients with squamous NSCLC could potentially benefit from the antitumor efficacy of bevacizumab without the associated bleeding risks (Kris 2005).

A small phase II trial [Bevacizumab and Chemotherapy for Operable NSCLC (BEACON)] has recently opened at Memorial Sloan-Kettering Cancer Center (MSKCC), exploring the use of cisplatin, docetaxel plus bevacizumab versus cisplatin and docetaxel alone as neoadjuvant therapy prior to surgical resection and bevacizumab maintenance therapy in patients with stage IA–IIIA operable NSCLC (Kris 2005). In addition, a large ECOG intergroup trial of chemotherapy plus bevacizumab versus chemotherapy alone as adjuvant therapy following complete surgical resection in patients with stage IB–IIIA NSCLC began in spring 2006.

Dosage, administration, and formulation

Bevacizumab (Avastin) should be given as an intravenous infusion of 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel (Anon. 2006). The drug should be discontinued in patients who experience gastrointestinal perforation, serious bleeding, delayed wound healing, thromboembolic event, nephrotic syndrome, hypertensive crisis, or RPLS, in whom antihypertensive treatment should also be initiated if hypertension is present.

Place in therapy

For more than a decade, platinum-based chemotherapy doublets have been the standard of care for patients with wet IIIB/stage IV NSCLC, offering only modest improvements in survival compared with best supportive care. Now, based on the first interim analysis of data from a phase II/III trial (Tyagi 2005), bevacizumab is set to dramatically influence the treatment of wet IIIB/stage IV NSCLC. In this study, the addition of bevacizumab to carboplatin/paclitaxel chemotherapy significantly improved the response rate, progression-free survival, and overall survival compared with chemotherapy alone (2-month survival advantage). Consequently, the combination of bevacizumab, carboplatin, and paclitaxel is already the ECOG reference standard for the first-line treatment of wet IIIB/stage IV nonsquamous NSCLC exclusive of squamous cell histology. Treatment guidelines will therefore require updating to take into account the benefits of bevacizumab in fulfilling the previously unmet need for an agent to improve survival in this group of patients with poor prognosis. Indeed, in October 2005, the National Comprehensive Cancer Network (NCCN) released newly updated clinical practice guidelines (NCCN 2006) to include bevacizumab combined with chemotherapy as first-line treatment for advanced NSCLC, based on the results of the phase II/III trial (Sandler et al. 2005a,b) investigating bevacizumab ± carboplatin plus paclitaxel in patients with previously untreated wet IIIB and stage IV NSCLC. Bevacizumab was approved in October 2006 for first-line use in combination with carboplatin and paclitaxel in patients with unresectable, locally advanced, recurrent, or metastatic NSCLC.

The synergistic antitumor efficacy of bevacizumab in combination with chemotherapy is thought to be due not only to the antiangiogenic effects of the drug, but also the reduction in vascular permeability, which in turn reduces tumor interstitial pressure, enabling chemotherapy drugs to penetrate the tumor more efficiently (Jain 2005).

Preliminary phase I/II data also suggest that bevacizumab combined with the HER-1/EGFR inhibitor erlotinib is well tolerated and could potentially improve outcomes in patients with nonsquamous NSCLC who have relapsed following first-line platinum-based chemotherapy. The results of the ongoing, randomized, phase III trial of bevacizumab plus erlotinib versus erlotinib monotherapy in the second-line treatment of wet IIIB/ stage IV nonsquamous NSCLC will be instrumental in determining the potential for bevacizumab plus erlotinib in this indication (Table 7).

The encouraging results obtained with bevacizumab in the treatment of advanced, inoperable NSCLC has challenged investigators to start exploring the wider use of this drug in patients with earlier-stage, operable disease. As angiogenesis is an essential component of wound healing, the timing of bevacizumab therapy relative to surgery is likely to be critical in minimizing postoperative wound healing complications. Experience with bevacizumab in the adjuvant treatment of patients with colorectal cancer (Scappaticci et al. 2004) indicates that treatment with bevacizumab should not be initiated for at least 28 days following major surgery, and not until the surgical wound has healed.

Bleeding events (in particular serious pulmonary hemorrhage) are the main safety concern associated with bevacizumab in the treatment of NSCLC. The currently available evidence indicates that patients with NSCLC classified as having squamous cell histology should not receive bevacizumab as they are at increased risk of potentially life-threatening bleeding episodes. It is important to note that the phase II/III pivotal trial investigating bevacizumab combined with carboplatin/paclitaxel chemotherapy assessed tumors of mixed histology by their predominant cell type. However, as discussed, bevacizumab could in concept be useful in patients with squamous NSCLC tumors for the postsurgical treatment of MRD, as bevacizumab-induced bleeding is thought to be due to tumor disintegration, rather than clotting disturbances.

Bevacizumab may also have potential in combination with radiotherapy in NSCLC. The antitumor efficacy of ionizing radiation is dependent on the tumor tissue being sufficiently oxygenated. The chaotic nature by which the tumor vasculature is laid down results in suboptimal delivery of oxygen to the tumor and areas of relative hypoxia that are resistant to the therapeutic effects of ionizing radiation. Inhibition of VEGF with bevacizumab normalizes the tumor vasculature (Poon et al. 2001), ensuring more effective tumor oxygenation, which in turn is likely to enhance the antitumoral effects of radiotherapy. Of interest, a series of studies conducted in animal models of human tumors demonstrated that bevacizumab and radiotherapy combined resulted in a greater delay in tumor growth, compared with either bevacizumab alone or radiotherapy alone (Hoang et al. 2005a,b). These encouraging data warrant clinical studies to investigate the potential for bevacizumab to augment the efficacy of radiotherapy for NSCLC in clinical practice.

Antiangiogenic agents are hypothetically less susceptible to multi drug resistance mechanisms than cytotoxic agents because they target the tumor vasculature, rather than the tumor itself. However, tumors are fully capable of circumventing the antiangiogenic effect of a single agent by utilizing alternative angiogenic pathways. It therefore seems likely that combinations of antiangiogenic agents targeting different angiogenic pathways will prove to be clinically advantageous in the future (Kris 2005).

In addition, it has been hypothesized that the combination of a VEGF inhibitor such as bevacizumab and a VEGFR tyrosine kinase inhibitor will produce supraadditive antitumor efficacy in patients. This hypothesis is supported by the results of a phase I study of sorafenib (a VEGFR tyrosine kinase inhibitor) combined with bevacizumab in patients with advanced solid tumors (Posadas et al. 2005a,b).

Overall, the current evidence base suggests that bevacizumab could have a significant impact on the treatment of NSCLC. Rigorous patient selection will be required to minimize bleeding risks, and analysis of prognostic factors is likely to facilitate the identification of patients who are most likely to benefit from bevacizumab therapy, thus enabling a more individualized approach to patient care. This approach may be particularly necessary to ensure the most cost-effective use of the drug.

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