Abstract. A plateau has been reached in the efficacy of cytotoxic chemotherapy for non-small cell lung cancer (NSCLC), highlighting the need for novel treatments for this poor-prognosis malignancy. Antiangiogenic agents, including the approved vascular endothelial growth factor (VEGF)-targeted monoclonal antibody, bevacizumab, as well as a number of investigational tyrosine kinase inhibitors (TKIs) that simultaneously target multiple angiogenic pathways, have demonstrated activity in patients with NSCLC. However, unlike the epidermal growth factor receptor (EGFR) TKIs erlotinib and gefitinib, for which the presence of EGFR-activating mutations are now known to predict response, no validated markers currently exist for the efficacy of antiangiogenic agents. Hypertension has been associated with antiangiogenic therapy and has also been evaluated as a surrogate marker for efficacy with this class of agents, although analyses, to date, have yielded conflicting results. This review provides a summary of currently available, clinically relevant data on the incidence of hypertension with VEGF-targeted antibodies and multitargeted antiangiogenic TKIs in advanced NSCLC and discusses the potential predictive role of hypertension on antiangiogenic therapy in such patients.

Antiangiogenic therapies have demonstrated activity across a multitude of malignancies, including colon cancer, renal cell carcinoma, breast cancer, and non-small cell lung cancer (NSCLC) (1). This efficacy, however, comes at the expense of increased toxicity, which includes risks of poor wound healing, bleeding, thrombosis, and proteinuria (2). A biomarker to identify which patients are most likely to derive benefit from antiangiogenic strategies could allow for an improved therapeutic ratio for these agents, but to date, none have been validated. Treatment-emergent hypertension has been associated with improved outcomes for some patients treated with antiangiogenic agents. While this is not as ideal as a biomarker that can be assessed prior to treatment initiation, if validated as predictive, monitoring for the development of hypertension could allow for early stratification of patients likely to benefit from continuation of antiangiogenic treatment. Establishment of a surrogate marker for efficacy may also allow for more efficient selection of new agents in this class. This review focuses on evidence, to date, from evaluation of treatment-emergent hypertension, as a surrogate marker for the efficacy of antiangiogenic therapies for NSCLC.

Bevacizumab (Avastin; Genentech, South San Francisco, CA, USA), a monoclonal antibody targeting the vascular endothelial growth factor (VEGF) ligand, was the first antiangiogenic agent approved for malignancy treatment (3). VEGF is the most widely studied pro-angiogenic growth factor, with an established role in the development and progression of malignancy (4, 5). Binding of bevacizumab to VEGF disrupts interaction of the ligand with the VEGF receptor (VEGFR), thereby preventing downstream signaling and ultimately inhibiting angiogenesis (6). In 2004, bevacizumab was approved by the US Food and Drug Administration (FDA) for the treatment of advanced colon cancer after demonstrating a survival benefit in combination with chemotherapy (3, 7).

For more than a decade, it is known that cytotoxic chemotherapy improves overall survival (OS) in advanced NSCLC, but the prognosis for these patients remains poor (8). Modern platinum-based chemotherapy doublets had reached an efficacy plateau (9, 10), so research efforts focused on the introduction of novel, targeted agents. It was not until the addition of bevacizumab to first-line chemotherapy in the Eastern Cooperative Oncology Group (ECOG) 4599 study that
a statistically significant survival benefit was demonstrated from the addition of a novel agent to standard chemotherapy (11). This randomized, phase III trial compared carboplatin and paclitaxel alone or in combination with bevacizumab at 15 mg/kg. Patients treated on the bevacizumab arm had a 21% reduction in risk of death [hazard ratio (HR)=0.79; p=0.003] and a two-month improvement in median survival versus carboplatin/paclitaxel (from 10.3 to 12.3 months) (11). Bevacizumab-treated patients also experienced improved tumor response rates (RRs) and superior progression-free survival (PFS). Currently, bevacizumab is FDA-approved for the first-line treatment of unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC in combination with carboplatin and paclitaxel (3).

Inhibitors of the epidermal growth factor receptor (EGFR) have also demonstrated an improvement in survival of patients with NSCLC, both when used alone (e.g. erlotinib) (12) and in combination with cytotoxic chemotherapy (e.g. cetuximab) (13). While there are clear biomarkers for predicting the efficacy of EGFR-targeted agents in NSCLC, including EGFR-activating mutations (14, 15) and potentially immunohistochemical staining for EGFR (13, 16), biomarkers that are predictive of the efficacy of antiangiogenic agents remain elusive. Based on the results of a phase II study in which an unacceptable rate of fatal pulmonary hemorrhage was observed with bevacizumab/chemotherapy among patients with squamous NSCLC, histology remains an important factor in terms of safety in the selection of patients who receive bevacizumab (17). This risk of fatal pulmonary hemorrhage also exists, albeit at a low rate of 1% to 2% (11), in patients with non-squamous histology; as a result, there has been increasing interest in patient selection so that those unlikely to benefit are not exposed to this risk.

There are a number of small-molecule, multitargeted tyrosine kinase inhibitors (TKIs) that inhibit the VEGF signaling pathway through inhibition of the VEGFRs 1, 2, and 3. Three such agents have been approved for use in the treatment of malignancies but are not approved for NSCLC: sorafenib (18), sunitinib (19), and pazopanib (20). These TKIs inhibit not only VEGFRs but also other angiogenic and proliferative pathways, such as platelet-derived growth factor (PDGF) (21), basic fibroblast growth factor (bFGF) (22, 23), v-raf murine sarcoma viral oncogene homolog B1 (BRAF) (24), stem cell factor receptor (KIT), and fms-like tyrosine kinase-3 (FLT-3) (25). In addition to contributing to tumor angiogenesis in their own right, the PDGF and FGF pathways have also been implicated in resistance to VEGF-targeted therapy (26, 27).

All inhibitors of the VEGF signaling pathway appear to cause hypertension as an adverse effect, and it has been suggested that the development of hypertension may be a surrogate marker of efficacy. The mechanism by which hypertension is induced by these agents is uncertain, although considering the VEGF pathway is known to regulate vasodilation (28), it logically follows that inhibition of this pathway could lead to vasoconstriction and hypertension (29). Proposed mechanisms through which VEGF inhibition may lead to hypertension include signaling related to the VEGFR-1 protein (30, 31) and the vasodilators prostaglandin I-2 (PGI2) and nitric oxide (NO) (28, 30). Blockade of the VEGF signaling pathway leads to a decrease in nitric oxide production, causing vasculature constriction and a reduction in the renal excretion of sodium, potentially leading to an increase in blood pressure (32, 33). Hypertension may also be a consequence of vascular rarefaction, which is the depletion of arterioles and capillaries caused by the inhibition of the growth factors required to form new capillaries and recruit endothelial cell progenitors (2, 34-36). The mechanism of these growth factors required to form new capillaries and recruit endothelial cell progenitors (2, 34-36). The mechanism by which antiangiogenic therapy causes proteinuria (33), there is also evidence that this may occur independently (37).

Hypertension has been evaluated as a surrogate marker for the efficacy of antiangiogenic agents, with results from analyses, to date, yielding mixed findings (38, 39). Analyses in advanced renal cell carcinoma suggest that treatment-emergent hypertension may predict outcomes (39). However, patients with renal cell cancer are likely to be unique in their propensity for hypertension, based on their disease pathophysiology, hence extrapolation of this finding to other malignancies is not necessarily warranted (40). Hypertension has also appeared to be predictive of outcome in other treatment settings, such as bevacizumab-treated colon cancer (41-44), glioblastoma (45), and sunitinib-treated gastrointestinal stromal tumors (46). In patients with metastatic breast cancer treated with bevacizumab and paclitaxel, those patients with grade 3/4 hypertension had significantly longer OS relative to those who did not experience hypertension (47). However, a study of bevacizumab in glioblastoma failed to demonstrate a correlation between hypertension and outcome (48).

This review provides a summary of data on the association of hypertension with VEGF-targeted antibodies and the various multitargeted TKIs, with a focus on evidence for the role of hypertension as a surrogate for efficacy in advanced NSCLC. Molecular targets of agents for which phase III trials in advanced NSCLC are completed or ongoing are summarized in Table I.

Incidence of Hypertension on Antiangiogenic Therapy for NSCLC

Antibody-based therapies. There have been two published articles on phase III trials of chemotherapy alone or with bevacizumab in advanced NSCLC. The first, as previously
discussed, was ECOG 4599 (11). In this study (N=878), patients with recurrent or advanced non-squamous NSCLC were randomized to receive either carboplatin/paclitaxel alone or in combination with bevacizumab at 15 mg/kg. Patients underwent a total of six cycles of chemotherapy alone or with bevacizumab, and in the absence of disease progression, those randomized to the bevacizumab arm continued to receive maintenance bevacizumab every three weeks until disease progression. The incidence of grade 3/4 hypertension in ECOG 4599 was significantly higher in the bevacizumab arm, compared with chemotherapy-alone (7% versus 0.7%, respectively; p<0.001) (11). In the AVAiL trial (N=1,043), patients with recurrent or advanced non-squamous NSCLC received either cisplatin/gemcitabine-alone or with one of two dose levels of bevacizumab, either 7.5 mg/kg or 15 mg/kg (49). The incidence of grade ≥3 hypertension was 6% with bevacizumab at 7.5 mg/kg, 9% with the 15 mg/kg dose, and 2% with chemotherapy-alone (49).

Meta-analyses have described an increased risk of hypertension during treatment with bevacizumab. In a meta-analysis of hypertension with bevacizumab among various malignancies (N=1,850 patients across seven studies, including a phase II trial in NSCLC), the relative risk of all-grade hypertension was 3.0 [95% confidence interval (CI)=2.2-4.2; p<0.001] for bevacizumab 7.5 mg/kg and 7.5% (95% CI=4.2-13.4; p<0.001) for bevacizumab at 15 mg/kg (50). In a continuous-dose study of sunitinib consisting of portions of the extracellular domains of human VEGF-1 and VEGF-2 fused to the Fc portion of human immunoglobulin G. In a phase I, dose-escalation trial of aflibercept in various types of advanced solid tumor (N=47), the incidence of all-grade hypertension was 38.3%, which was mostly grade 3 in severity (n=13) (50).

Multitargeted TKIs. Hypertension has also been reported with multitargeted TKIs that simultaneously inhibit multiple proangiogenic factors. Sorafenib (Nexavar®; Bayer, Leverkusen, Germany) was evaluated in combination with first-line carboplatin/paclitaxel in a phase III study in advanced NSCLC (ESCAPE; N=926) (51). This study was closed due to futility in reaching the primary end-point of improved OS. The observed incidence of grade 3/4 hypertension was 3% in the sorafenib arm compared with 1% in the chemotherapy-alone arm. The incidence of all-grade hypertension was 12% in the sorafenib arm versus 6% in chemotherapy-alone (p<0.001) (51). In a meta-analysis of hypertension with sorafenib among various malignancies (N=4,599 across nine studies, including a phase II trial in NSCLC), the incidence of all grade and grade 3/4 hypertension was 23.4% and 5.7%, respectively (52).

Sunitinib (Sutent®, Pfizer, New London, CT, USA) has been evaluated in phase II trials in NSCLC. On an intermittent dosing schedule of 4 weeks on and 2 weeks-off in patients with pre-treated advanced NSCLC (N=63), the incidence of all-grade and grade 3 hypertension was 11% and 5%, respectively (53). In a continuous-dose study of sunitinib in previously treated advanced NSCLC (N=47), the incidence of all-grade hypertension was 28% and that of grade 3 hypertension was 9% (54). Finally, in a meta-analysis of
hypertension with sunitinib across various malignancies (N=4,999 patients across 13 studies, including two phase II trials in NSCLC), the incidence of all-grade and grade 3/4 hypertension was 21.6% and 6.8%, respectively (55).

In a phase II trial (N=35) of single-agent, pazopanib (Votrient; GlaxoSmithKline, London, UK), as neoadjuvant therapy for stage I/II resectable NSCLC, hypertension was the most common adverse event (43% incidence) but was limited to grade 1/2 severity (56).

Vandetanib (Zactima; AstraZeneca, Wilmington, DE, USA) is no longer being studied in advanced NSCLC due to futility, based on the results of several large phase III clinical trials (57-60). In the ZEPHIR phase III trial (N=924), the incidence of all-grade hypertension was 26% among patients receiving vandetanib versus 3% receiving placebo (57). In a phase III trial of second-line vandetanib plus pemetrexed versus pemetrexed alone (ZEAL; N=534), all-grade hypertension occurred in 12% of those receiving vandetanib versus 3% of those receiving chemotherapy-alone (58). In another phase III trial of second-line docetaxel-alone or with vandetanib (ZODIAC; N=1,391), all-grade hypertension was reported in 6% of patients in the vandetanib arm versus 2% of patients who received docetaxel-alone (60). The corresponding grade 3 incidence of hypertension was 0.9% with vandetanib and 0.1% with docetaxel-alone (60). In a phase III trial of single-agent vandetanib versus erlotinib in NSCLC (N=1,240), the incidence of all-grade hypertension was 16% with vandetanib versus 2% with erlotinib (59).

Nintedanib (BIBF 1120; Boehringer Ingelheim, Ingelheim, Germany) may have a lower propensity for causing hypertension relative to other multitargeted TKIs. In a phase I study of nintedanib in combination with pemetrexed as second-line therapy for advanced NSCLC (N=26), there was one reported case of grade 1 hypertension (61). In a phase II trial of two doses of single-agent nintedanib in advanced, previously-treated NSCLC (ZEST; N=1,240), the incidence of all-grade hypertension was 16% with nintedanib versus 2% with erlotinib (59).

In the first study to model blood pressure over time in patients with NSCLC, Dahlberg et al. performed a retrospective analysis of ECOG 4599 to examine the hypothesis that the onset of hypertension during treatment denotes successful blockage of the VEGF pathway and is therefore correlated with an improved outcome (66). The primary analysis classified patients as being hypertensive if blood pressure during cycle 1 ever exceeded 150/100, or if diastolic blood pressure increased at the end of the first cycle by >20 mmHg from baseline. Of the 850 patients enrolled on ECOG 4599, eligible for inclusion, 106 patients had missing blood pressure measurements at baseline or at the end of cycle 1, and three patients had progressive disease or death prior to the end of cycle 1. Therefore, 741 patients were included in the primary analysis. There were no differences in baseline blood pressure measurements between patients in the bevacizumab arm versus those in the chemotherapy arm. No differences in survival by blood pressure status were observed within the chemotherapy arm, indicating hypertension was not a predictive factor in this study. On multivariate analysis, bevacizumab-treated patients who developed hypertension did have a significantly longer OS and PFS compared with those who did not develop hypertension (OS=15.9 versus 11.5 months, p=0.0002; PFS=7.0 versus 5.5 months, p<0.0001; Figure 1).
However, in a formal test for treatment by blood pressure interaction, statistical significance was not reached, and the authors noted that this analysis was not sufficiently powered to evaluate the predictive value of hypertension. In addition, ECOG 4599 did not require reporting of grade 1/2 hypertension or blood pressure changes that were not unexpected or considered at least possibly treatment-related (66).

In a retrospective analysis of the BR24 trial of first-line carboplatin/paclitaxel with and without cediranib in advanced NSCLC, the association between hypertension and efficacy was explored (67). The definition utilized included both new-onset hypertension and worsening hypertension (in patients with pre-existing hypertension). The development of hypertension was associated with a reduced risk of death in both the cediranib arm (HR=0.62; 95% CI=0.38-1.03; p=0.06) and the placebo arm (HR=0.49; 95% CI=0.30-0.80; p=0.0045). For both arms combined, hypertension was an independent predictive factor for better OS (HR=0.7; 95% CI=0.5-1.0; p=0.06). Landmark analyses at the end of cycles 1 and 2 demonstrated improved OS among hypertensive patients in both arms (Figure 2). However, development of hypertension in this study did not predict benefit from cediranib (67).

Additional smaller studies and retrospective analyses have evaluated the potential predictive value of hypertension with bevacizumab treatment. A recent retrospective chart review (N=454; n=104 with lung cancer) stratified patients treated with bevacizumab by hypertension status: group A developed hypertension or required an increase in antihypertensives during treatment with bevacizumab; group B did not develop hypertension or did not require increased antihypertensives during treatment with bevacizumab (68). The median OS was significantly prolonged in group A versus group B (607 days versus 355 days, p<0.0001). The median PFS was also significantly prolonged in group A versus group B (197 days versus 117 days, p<0.0001) (68). In addition, a recently published case series described six patients who developed hypertension and proteinuria on bevacizumab-containing treatment, all with prolonged PFS (69). One of these patients had NSCLC and experienced a PFS of >6 months with bevacizumab/pemetrexed (69).

A retrospective analysis of data from five phase II trials of axitinib (N=230; n=30 patients with NSCLC), focused on the relationship between diastolic blood pressure ≥90 mmHg and efficacy (70). A pooled analysis, patients who developed a diastolic blood pressure ≥90 mmHg while on therapy had significantly prolonged OS compared with...
normotensive patients (25.8 versus 14.9 months, respectively; HR=0.55; 95% CI=0.39-0.77; p<0.001) and a significantly higher RR (43.9% versus 12.0%, respectively, p<0.001). PFS was also numerically prolonged in these patients compared with those who had diastolic blood pressure <90 mmHg (10.2 versus 7.1 months, respectively; HR=0.76; 95% CI=0.54-1.06; p=0.107). Specific analysis of patients with NSCLC showed that median OS was not reached for patients with diastolic blood pressure ≥90 mmHg versus 12.8 months for patients without diastolic blood pressure ≥90 mmHg (70).

Discussion

Because hypertension is a treatment-emergent adverse event, its potential use as a surrogate marker for efficacy has inherent limitations (38). Currently, there are no known patient characteristics that predict for development of hypertension during antiangiogenic therapy. While genetic polymorphisms protecting against or predisposing patients to antiangiogenic therapy-induced hypertension have been described (47, 71, 72), the clinical applicability of these are
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as yet uncertain. Because the earliest time point for detecting antiangiogenic therapy-induced hypertension may be as early as the first day of treatment, monitoring would need to begin immediately upon treatment initiation (73, 74). Notably, the relative importance of early versus later blood pressure changes is also unknown (38).

Under real-world conditions, there are numerous shortcomings that could limit the implementation of blood pressure monitoring as a potential surrogate for antiangiogenic therapy efficacy. Repeated measurements in the clinical setting may not reflect true hypertension status, and therefore patients may require ambulatory blood pressure monitoring (40, 75). Additional confounding factors are the differing definitions of hypertension utilized and the unknown impact of patient history of antihypertensive management on its potential predictive value. Analyses to date have focused on patients who either do or do not develop hypertension, and the relevance of blood pressure elevations that remain within the normal range is uncertain (40).

Dosing to hypertension is an intriguing concept for antiangiogenic agents, but one for which validation is lacking. An analysis of blood pressure changes in a mixed solid tumor population treated with varying doses of sorafenib did not support a dose-to-hypertension approach to increasing activity (76). The dose escalation utilized in this study did not lead to a consistent elevation in diastolic blood pressure.

Conclusion

Hypertension is a common adverse event of therapy with antiangiogenic agents. However, hypertension may not be a true class effect as the incidence and severity varies across agents. Available evidence, albeit limited, suggests that hypertension does not represent a surrogate for the efficacy of antiangiogenic therapy in advanced NSCLC. Indeed, agents that caused considerable hypertension, such as vandetanib and sorafenib, did not show sufficient efficacy for continued development in NSCLC. Ongoing investigation of antiangiogenic agents and the association between efficacy and various biomarkers, including hypertension, is nevertheless in order.

Conflicts of Interest

Dr. Evans has served as a consultant for Genentech and Lilly.

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