Vascular Endothelial Growth Factor Trap in Non–Small Cell Lung Cancer

Gregory J. Riely and Vincent A. Miller

Abstract

Several drugs currently in development target the vascular endothelial growth factor (VEGF) pathway, a validated target in the treatment of non–small cell lung cancer (NSCLC). Most clinical trial data generated to date have been with either bevacizumab, a monoclonal antibody to VEGF, or small-molecule inhibitors of VEGF receptor (VEGFR) tyrosine kinase activity (sunitinib, sorafenib, and ZD6474). VEGF Trap, an engineered soluble receptor made from extracellular domains of VEGFR1 and VEGFR2, binds to all isoforms of VEGF and to placental growth factor. VEGF Trap binds to VEGF-A and VEGF-B with markedly higher affinity than bevacizumab. The toxicities seen in phase I trials of s.c. and i.v. administration of VEGF Trap, hypertension and proteinuria, are similar to those seen with other molecules that target the VEGF pathway. In the s.c. VEGF Trap phase I trial, significant radiographic improvement was observed in a patient with heavily pretreated NSCLC. Ongoing phase I trials are evaluating combinations of VEGF Trap with platinum-based doublets and single-agent docetaxel. The activity of single-agent VEGF Trap in NSCLC is being assessed in a multicenter phase II trial.

Current Treatment of Patients with Metastatic Non–Small Cell Lung Cancer

Patients with metastatic non–small cell lung cancer (NSCLC) benefit from treatment with palliative chemotherapy (1). Multiple trials comparing chemotherapy to best supportive care have shown that, in the first-line and second-line settings, patients treated with chemotherapy have improved overall survival and improved quality of life. Further work has shown that combination therapy with two standard chemotherapeutics improves response rate and survival compared with single-agent chemotherapy (2). Although combinations of three cytotoxic chemotherapeutics can further improve response rate, there is no associated improvement in survival over two-agent regimens and there is an increase in observed toxicity (2). More recently, investigators have examined the addition of targeted therapies to standard chemotherapeutics. The combination of chemotherapy with the epidermal growth factor receptor inhibitors gefitinib and erlotinib failed to show any improvement in overall survival when compared with chemotherapy alone (3–6). The first targeted therapy to show a survival advantage in combination with standard chemotherapy was bevacizumab, a monoclonal antibody directed at vascular endothelial growth factor (VEGF; ref. 7).

VEGF and VEGFR

The VEGF pathway is the best-characterized pathway governing angiogenesis in normal human development (Fig. 1; reviewed in ref. 8). Multiple lines of evidence suggest that VEGF and its receptors may have altered activity in human cancer (9). The ligands of the VEGF pathway include multiple isoforms of VEGF-A, VEGF-B, and placental growth factor. There are at least three known receptors for VEGF with different binding affinities, tissue distributions, and cellular functions. The functions of VEGFR1 include induction of matrix metalloproteinases, regulation of hematopoiesis, and recruitment of monocytes. VEGFR2, a receptor with higher affinity and greater kinase activity, is more important in the direct regulation of angiogenesis, mitogenic signaling, and permeability-enhancing effects. VEGFR3 is responsible for the growth, development, and maintenance of lymphatics.

Anti-VEGF Treatment in NSCLC

Bevacizumab, a monoclonal antibody to VEGF-A, is the best-studied anti-VEGF therapy in NSCLC. In Eastern Cooperative Oncology Group 4599, investigators randomly assigned 878 patients with nonsquamous NSCLC to either carboplatin and paclitaxel or the same regimen with bevacizumab (15 mg/kg every 3 weeks). Among the 773 patients with measurable disease, the addition of bevacizumab improved the response rate from 15% to 35% (see Table 1). Median progression-free survival improved by 1.7 to 6.2 months and median overall survival improved from 10.3 to 12.3 months. Following Food and Drug Administration approval in October of 2006, bevacizumab in combination with carboplatin and paclitaxel has become a standard of care as first-line treatment in patients who met eligibility requirements for Eastern Cooperative Oncology Group 4599.
Patients with brain metastases, squamous histology, and those requiring anticoagulation were excluded from Eastern Cooperative Oncology Group 4599 as a result of bleeding events seen in earlier trials of bevacizumab in NSCLC (10). In the randomized phase II trial of bevacizumab and chemotherapy that explored carboplatin and paclitaxel in combination with 7.5 mg/kg bevacizumab or 15 mg/kg bevacizumab every 3 weeks, squamous histology patients were included. Although patients with squamous histology represented only 20% of patients included in the trial, four of six patients with major life-threatening bleeding (described as hemoptysis or hematemesis) had squamous carcinomas. The incomplete safety data for bevacizumab in patients not eligible for Eastern Cooperative Oncology Group 4599 may represent an opportunity for drug development in these populations.

Further evidence of a role for VEGF inhibition in NSCLC comes from trials of several multitargeted, small-molecule tyrosine kinase inhibitors. Preliminary data indicate that treatment with sunitinib, a small-molecule inhibitor of VEGFR1, VEGFR2, VEGFR3, platelet-derived growth factor receptor α and β, RET, KIT, and FLT-3, led to a 10% response rate, median progression-free survival of 11 weeks, and median overall survival of 24 weeks in 63 previously treated patients with metastatic NSCLC (11). These results are not dissimilar from those reported with approved cytotoxic chemotherapy in previously treated patients. Treatment with sorafenib, an inhibitor of VEGFR1, VEGFR2, VEGFR3, platelet-derived growth factor receptor β, FLT-3, KIT, and p38, was associated with a 3-month median progression-free survival and a 7-month median overall survival in patients with previously treated NSCLC (12). Although some tumor regression was observed, no confirmed Response Evaluation Criteria in Solid Tumors partial responses were observed with this agent. Finally, ZD6474, an inhibitor of VEGFR2 and epidermal growth factor receptor studied in a randomized, blinded crossover trial along with gefitinib, showed a response rate of 8% and a median progression-free survival of 11 weeks (13). ZD6474 is currently being evaluated in a phase III trial comparing docetaxel alone with ZD6474 with docetaxel. Taken together, the modest success of these agents alone and with chemotherapy confirms the validity of targeting the VEGF pathway.

The various approaches to VEGF pathway-directed therapies have similar toxicities. The toxicities of greatest concern are episodes of hemorrhage. Although patients with brain metastases have been excluded from most of these trials to avoid the risks associated with central nervous system hemorrhage, pulmonary hemorrhage has been seen in the trials with bevacizumab, sorafenib, and sunitinib, with many of these events fatal (7, 11, 12). Other toxicities that are common to these agents include hypertension and proteinuria.

### Mechanism of Anti-VEGF Therapy

Several mechanisms have been postulated to explain the observed antitumor activity of anti-VEGF treatments given alone and in combination with chemotherapy (reviewed in refs. 14–16). The simplest hypothesis is that anti-VEGF therapies directly inhibit tumor cell growth. Work from several animal models suggests that anti-VEGF therapies can inhibit the growth of existing tumor blood vessels as well as block the growth of new vessels. Finally, recent clinical data support the hypothesis that anti-VEGF therapy leads to tumor vessel “normalization,” which allows more effective treatment with chemotherapy or radiation therapy (17, 18). There has been little clinical work to explore the mechanism of action of anti-VEGF therapy in patients with NSCLC.

### Development of VEGF Trap

VEGF Trap is a soluble receptor to VEGF developed by Regeneron, Inc. Etanercept (Enbrel, Immunex), a conceptually similar molecule made up of soluble receptors to tumor necrosis factor-α, is an effective treatment for rheumatoid arthritis and is Food and Drug Administration approved for treatment of several rheumatologic disorders (19). VEGF Trap is a high-affinity anti-VEGF compound, engineered by combining domains from VEGFR2 and VEGFR1. Initial animal data with ZD6474 with docetaxel. Taken together, the modest success of these agents alone and with chemotherapy confirms the validity of targeting the VEGF pathway.

### Table 1. Outcomes for trials of patients with NSCLC treated with bevacizumab

<table>
<thead>
<tr>
<th>RR (%)</th>
<th>PFS/TTP*</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al. 1</td>
<td>19</td>
<td>4.2</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel</td>
<td>28</td>
<td>4.3</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel/bevacizumab (7.5 mg/kg)</td>
<td>32</td>
<td>7.4</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel/bevacizumab (15 mg/kg)</td>
<td>35</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Abbreviations: RR, response rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival.

1 For Johnson et al., time to progression is reported; for Sandler et al., progression-free survival is reported.

1 Response rate and time to progression are based on investigator assessment.
revealed that soluble VEGFR had poor bioavailability when administered s.c. These characteristics were hypothesized to be related to a high positive charge of the protein, which led to deposition of Trap molecules at the s.c. injection site due to nonspecific adhesion to components of the extracellular matrix. To overcome this issue (Fig. 2), investigators removed the third Ig domain of VEGFR1 (with significant basic charge), replaced it with the third Ig domain from VEGFR2, and added a dimerization domain from the Fc region of human IgG (20). These changes decreased the isoelectric point of VEGF Trap and increased bioavailability after s.c. administration, with an increase in $C_{\text{max}}$ and area under the curve of VEGF Trap. The structural changes introduced into VEGF Trap dramatically improved the affinity of the VEGF Trap molecule for VEGF-A, VEGF-B, and placental growth factor.

In equilibrium binding assays, VEGF Trap, with a molecular weight of 115 kDa, had an affinity for VEGF of $\sim 1$ pmol/L, significantly improved from the 5 pmol/L binding affinity seen with a Trap molecule made solely from VEGFR1 domains (20). In addition, VEGF Trap binds placental growth factor with an affinity of $\sim 45$ pmol/L. These values compare with the VEGF affinity of bevacizumab of $\sim 500$ pmol/L. The importance of binding affinity and spectrum of binding has not been clearly defined; however, the goal of depleting tissue and plasma VEGF is hypothesized to be better accomplished through higher affinity.

**Preclinical Studies of VEGF Trap**

Several in vitro experiments have shown the potential antitumor efficacy of VEGF Trap. Holash et al. (20) examined VEGF Trap in several tumor xenograft models (mouse B16F1O.9 melanoma, human A673 rhabdomyosarcoma, and rat C6 glioma cell lines). When given s.c. twice weekly, VEGF Trap led to significant decrease in tumor size for the xenografts tested when compared with control treated animals. Immunohistochemical staining showed a dramatic, dose-dependent reduction in tumor vasculature in the VEGF-treated mice. To achieve similar growth inhibition of B16F1O.9 cells with the anti-VEGFR2 antibody DC101, serum levels 60 times those of VEGF Trap were required. Fukasawa and Korc (21) looked at VEGF Trap treatment begun 2 days after implantation of four pancreatic cancer cell lines in athymic nude mice. In that work, VEGF Trap treatment led to suppression of growth in all four cell lines and was accompanied by a significant reduction of tumor microvessel density.

To explore the effect of VEGF Trap on established tumors, Huang et al. (22) studied neuroblastoma xenografts. Five weeks after implantation, at which point large retroperitoneal tumors had formed, mice were treated with VEGF Trap by i.p. injection biweekly. Whereas tumors treated with control protein continued to grow, treatment with VEGF Trap led to a 79% decrease in mean tumor weight after just 36 days of treatment. In vivo fluorescein imaging of tumor vasculature showed a marked decrease in vessel density just 1 day after treatment with VEGF Trap. For metastatic lesions, whereas the number of metastatic lung tumors did not change significantly, the mean tumor diameter decreased by 80%, mean volume decreased by 78%, and mean cell count per tumor decreased by 83%. This unique ability to induce tumor regression may reflect the high-affinity binding of VEGF Trap to VEGF.

Other investigators have examined combination treatment with VEGF Trap and conventional cytotoxic chemotherapy. Hu et al. (23) examined the efficacy of VEGF Trap in combination with paclitaxel. In an ovarian cancer xenograft model, they showed >50% decrease in tumor burden with either VEGF Trap or paclitaxel alone. Strikingly, the combination of VEGF Trap and paclitaxel (given thrice weekly) led to a 98% reduction in tumor volume with associated reduction in ascites. Correlative work showed significant decrease in tumor vasculature in the tumors treated with VEGF Trap and paclitaxel. Treatment with VEGF trap alone or paclitaxel alone resulted in only modest rates of apoptosis (10% and 40%, respectively), whereas the combination of VEGF Trap and paclitaxel led to apoptosis in >90% of tumor cells.

**Phase I Data for VEGF Trap**

The first phase I trial of VEGF Trap explored s.c. administration (24). In a dose escalation trial beginning at 25 μg/kg administered weekly with escalation to 800 μg/kg twice weekly, the maximum tolerated dose has not been reached. Preliminary toxicity data are consistent with inhibition of the VEGF pathway. The most common grade 3/4 toxicities were proteinuria, hypertension, venous thromboembolic disease, and leukopenia. Heavily pretreated patients (median prior treatment regimen $= 5$) with a variety of tumor types were enrolled (kidney, colon, ovary, lung, thymic tumors, and sarcoma). At the two highest dose levels reported (800 μg/kg weekly or twice weekly), 8 of 10 patients had stable disease for >10 weeks. Significant symptomatic and radiographic improvements were seen in a patient with lung cancer who had been resistant to prior treatment with cisplatin/gemcitabine, docetaxel/bortezomib, and erlotinib. I.v. VEGF Trap, given on an every-2-week schedule, showed similar results (25). Again, toxicities suggestive of VEGF inhibition were seen, such as grade 3/4 proteinuria, hypertension, fatigue, and hoarse voice. The maximum tolerated dose has not been reached at 5 mg/kg every 2 weeks. Partial responses were seen in patients with ovarian cancer and thymoma.

Pharmacokinetic data from the s.c. and i.v. VEGF Trap phase I trials indicate that, at doses of 800 μg/kg s.c. once weekly or
2 mg/kg i.v. every 2 weeks, concentrations of free VEGF Trap were in excess of bound VEGF Trap, suggesting adequate drug delivery to achieve maximal VEGF binding. These free/bound ratios have corresponded to anti-tumor efficacy in animal xenograft models. There has been no evidence of development of anti-VEGF Trap antibodies.

Ongoing Trials

Whereas dose escalation in the phase I trials continues, phase II trials in several diseases are ongoing, including ovarian cancer and NSCLC. Because symptomatic malignant ascites represents a significant problem for patients with ovarian cancer, VEGF Trap is being investigated in patients with advanced ovarian cancer in a randomized, placebo-controlled trial with a primary end point of time to repeat paracentesis. The phase II trial in NSCLC is a single-arm, single-agent, open-label, two-stage trial. Patients are treated with 4 mg/kg i.v. every 2 weeks. The 4 mg/kg every 2-week dose of VEGF Trap corresponds to a dose level above the dose at which free VEGF Trap was in excess of bound VEGF Trap in a phase I trial (see above). The primary end point for this trial is response rate using modified Response Evaluation Criteria in Solid Tumors (26). The response criteria were modified to account for cavitation, a radiographic change noted in many patients treated on trials of targeted agents. Due to concern about the safety profile of anti-VEGF treatments, patients with squamous histology tumors or brain metastases have been excluded from this trial.

Conclusions

Clinical trial data show that several drugs, with several different mechanisms of targeting the VEGF pathway, have an important role in the treatment of advanced NSCLC. The high affinity of VEGF binding and different ligand binding spectrum of VEGF Trap raise the possibility that VEGF Trap may have advantages over the current generations of VEGF-directed therapies. During the continued development of drugs targeting the VEGF/VEGFR pathway, it remains important to identify molecular, pathologic, and clinical correlates of treatment benefit to identify optimal treatment for individual patients.

Open Discussion

Dr. Thomas Lynch: In Dr. Heymach’s work with ZD6474, they are allowing patients with brain metastases. Many of the other VEGF kinase inhibitors that are being developed have allowed patients with brain metastases. So what was the thinking here in excluding them?

Dr. Roy Herbst: It is conservative management. You are right, all these agents can and probably should be studied in brain earlier rather than later. The other issue is the squamous cell carcinoma patients. I was very much against excluding those patients, but that is again conservative management, based on the data from the early bevacizumab work.

Dr. Lynch: How do people feel about these modified RECIST criteria?

Dr. Philip Bonomi: I think it is reasonable. The RECIST just does not capture these tumors that respond by cavitation, which may be an 80% reduction in volume.

Dr. Lynch: I think it is innovative and you should be applauded for it. We just have to be careful that the changes in criteria are not forgotten when the data come out and show a response rate of 30%, that it isn’t compared, for example, to the AZD2171 data that were shown earlier, where cavitation was scored as stable disease.

Dr. Mark Socinski: Or to the sorafenib response rate of zero, despite seeing cavitations.

Dr. Ramaswamy Govindan: You can have all these stellar responses, you can call it in a modified way. It is progression-free survival that finally matters.

Dr. John Heymach: With drugs that clearly cause cavitation responses, like imatinib and SU11248 for GIST, in the end the progression-free survival data sort out. It is at least theoretically possible that growing tumor becomes necrotic in the center and you may falsly read that as stable disease. Part of the natural progression of a tumor is that the core becomes progressively more hypoxic so cavitation does occur as part of tumor growth.

Dr. Lynch: Not to the degree that we have seen here, though, do you think?

Dr. Heymach: No, within the context of a trial where you are following patients, it would probably be rare, but you do have large tumors that suddenly become necrotic.

References

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