

Spectrum of Activity and Mechanism of Action of VEGF/PDGF Inhibitors

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Background: Angiogenesis plays an important role in tumor growth and metastasis.

Methods: We review the function of the vascular endothelial growth factor (VEGF) in vessel formation that is complemented by platelet-derived growth factor (PDGF). We also review the agents designed to target VEGF, PDGF, and/or their receptors.

Results: VEGF plays a central role in tumor angiogenesis. It is expressed at increased levels in colorectal, liver, lung, thyroid, breast, as well as in bladder, ovary, uterine cancers, and in angiosarcomas, germ cell tumors, intracranial tumors, and others. VEGF blockade has been shown to have a direct and rapid antivascular effect in both animal and human tumors, through deprivation of tumor vascular supply and inhibition of endothelial proliferation. Overexpression of PDGFs and their receptors has also been reported in many types of cancers such as prostate, ovarian, and non-small-cell lung cancer. Many VEGF and PDGF inhibitors are available. The use of some of these inhibitors has significantly improved the survival of cancer patients. Several agents are in development and currently are being tested in clinical trials.

Conclusions: Angiogenic agents inhibiting VEGF and PDGF have shown promising clinical results. Targeting more than one pathway by combining different agents may increase the antitumor activity of these drugs. The implementation of reliable radiologic and pathologic angiogenesis monitoring techniques is necessary to implement antiangiogenic therapies in cancer.

Introduction

The discovery of the vascular endothelial growth factor family and its receptors has provided insights into the role of angiogenesis in pathologies ranging from ischemic heart disease to cancer. In the early 1970s, Folkman et al¹ identified a tumor-angiogenesis factor that is mitogenic to capillary endothelial cells in human and animal solid tumors and suggested that blocking this factor might arrest tumors with a tiny diameter (few millimeters). This was later called vascular endothelial

growth factor (VEGF). Although prolongation of tumor dormancy by prevention of neovascularization and antiangiogenesis was reported in the mid 1970s, the direct association between the expression and angiogenic effects of VEGF and tumor growth did not become clear until the early 1990s.^{2,3}

Preclinical studies have justified the use of these agents in the clinic either as single agents or in combination with chemotherapy. VEGF plays an important role in tumor growth and metastasis. It is recognized as an essential regulator of normal and abnormal blood vessel growth. It regulates both vascular proliferation and permeability, and it functions as an anti-apoptotic factor for newly formed blood vessels. It is expressed in response to hypoxia, oncogenes, or cytokines, and its expression is associated with poor prognosis in several types of cancer.⁴ VEGF blockade has been shown to have a direct and rapid antivascular effect in both animal and human tumors, through deprivation of tumor vascular supply and inhibition of endothelial proliferation. The function of VEGF in vessel formation is complemented by platelet-derived growth factor (PDGF). PDGF signaling also indirectly regulates angiogenesis. PDGF receptor β can induce the transcription and secretion of VEGF. Compared with PDGF, VEGF has attracted more interest as a pos-

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Abbreviations used in this paper: VEGFR = vascular endothelial growth factor receptor, PDGFR = platelet-derived growth factor receptor, GIST = gastrointestinal stromal tumor, BV = bevacizumab, NSCLC = non-small-cell lung cancer.

sible therapeutic target since the role of PDGF in angiogenesis is not yet fully understood.

In mice, inhibiting PDGF receptors in combination with paclitaxel produced substantial therapeutic effects against prostate cancer bone metastasis.⁵ Also, in mice, inhibiting PDGF receptors with imatinib increased the level of apoptosis of endothelial cells but not tumor cells in a multidrug-resistant prostate cancer model, and it led to statistically significant decreases in bone tumor incidence.⁶ Many new agents designed to target VEGF, PDGF, and their receptors are already considered standard of care in the treatment of a variety of tumors (Table). Many others are in development and are being tested in clinical trials. This review addresses the role of VEGF and PDGF inhibitors in cancer treatment.

VEGF

In mammals, the VEGFs are encoded by a family of genes including VEGF-A, -B, -C, -D, and placental growth factor (PGF).⁷ VEGF-A, -B, and PGF are predominantly required for blood vessel formation, while VEGF-C and -D are essential for the formation of lymphatic vessels.⁸ The function of VEGFs in vessel formation is complemented by additional factors such as basic fibroblast growth factor (bFGF),⁹ transforming growth factor β (TGF- β),¹⁰ PDGFs,¹¹ and the angiopoietins.¹² VEGF plays a central role in tumor angiogenesis and is also expressed in colon and rectal cancers, liver, lung, thyroid, breast, gastrointestinal, bladder, ovarian and uterine cancers, angiosarcomas, and germ cell and intracranial tumors at increased levels.¹³

The biological functions of VEGF are mediated upon binding to receptor tyrosine kinases; VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4).¹⁴ VEGF receptors are closely related to Kit and PDGF receptors and are activated upon ligand-mediated receptor dimerization.¹⁵ VEGF-A binds to VEGFR-1 and -2, while VEGF-C and -D bind to VEGFR-2 and -3 (Fig 1). Receptor-specific interactions have been described for some VEGF variants: PGF and VEGF-B exclusively bind to VEGFR-1.^{16,17} Each receptor subtype assembles a different set of signaling molecules, giving rise to the formation of specific signal transduction at the plasma membrane. VEGFR-2 regulates endothelial cell migration, proliferation, differentiation, and survival as well as vessel permeability and dilation. VEGFR-2 is the predominant receptor in angiogenic signaling. Some signaling pathways activated by VEGFR-2 are the PI 3-kinase/Akt pathway¹⁸ and the classical Ras-dependent signaling cascade impinging on MAP kinases such as ERK1 and ERK2.^{19,20} Targeting these pathways in cancer has been the focus of recent research with encouraging results.

PDGF

The PDGFs are a family of peptide growth factors that signal through cell surface tyrosine kinase receptors and stimulate various cellular functions including growth, proliferation, and differentiation. Four different polypeptide chains (PDGF-A, -B, -C, and -D) that are encoded by different genes (chromosomes 4, 7, 11, 22) have been described.²¹⁻²⁴ Fibroblasts, keratinocytes,

Table. — VEGF and PDGF Inhibitors

Agent	TKI	VEGF	VEGFR	PDGFR	Bcl-Abl	C-kit	Flt-3	Raf	EGFR	FGFR
Bevacizumab		X								
Imatinib (STI157)	X			X	X	X				
Sorafenib (BAY439006)	X		X	X				X		
Sunitinib (SU11248)	X		X	X		X	X			
Leflunomide (SU101)	X			X					X	
Midostaurin (PKC412)	X		X	X		X				
Semaxanib (SU5416)	X		X	X						
Vatalanib (PTK787)	X		X	X		X				
AG013736	X		X	X		X				
AZD2171	X		X							
CDP860				X						
CP547,632	X		X							
CP673,451	X			X						
RPI.4610			X							
SU6668	X		X	X						
VEGF-trap		X								
ZD6474	X	X							X	
YM359445	X		X							

TKI = tyrosine kinase inhibitor, EGFR = epidermal growth factor receptor, FGFR = fibroblast growth factor receptor.

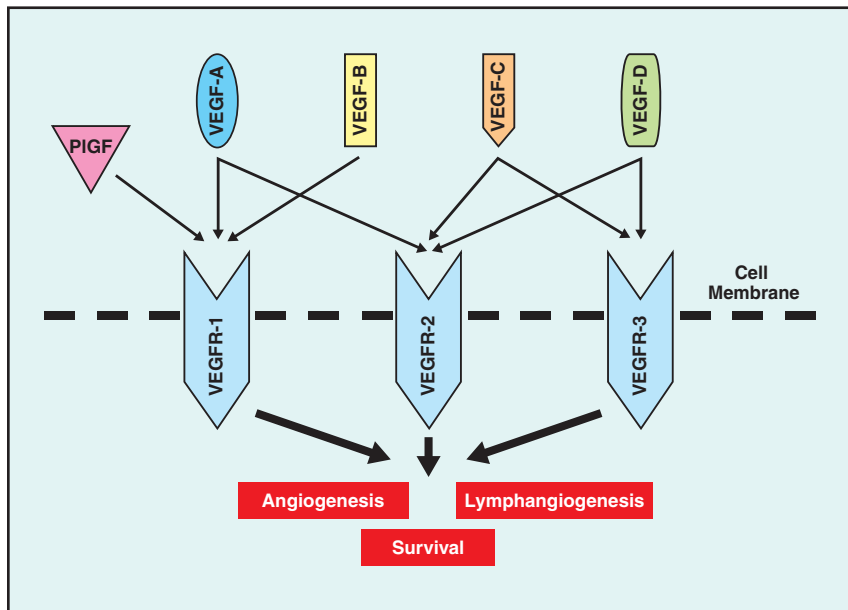


Fig 1. — VEGF Ligand and receptor interactions. PIGF = placental growth factor.

neurons, endothelial cells, and epithelial cells express PDGF.²⁵ The polypeptide chains are linked to form homodimers or heterodimers, of which five have been described: PDGF-AA, -AB, -BB, -CC, and -DD (Fig 2). These factors exert their cellular effects through PDGF- α and PDGF- β protein tyrosine kinase receptors. PDGFs activate their receptors by forming receptor dimers: PDGFR- $\alpha\alpha$, PDGFR- $\alpha\beta$, and PDGFR- $\beta\beta$.²⁶ The activated receptors phosphorylate a large number of substrates (more than 20), including themselves, initiating a complex network of signaling cascades. PDGFR- α and PDGFR- β distinctly activate downstream effectors such as Grb2/SOS, PI3K, GAP, Erk, JNK, Src, and Stat.²⁶ Uncontrolled PDGFR activation promotes cell migration, proliferation and survival.

PDGFRs are expressed on erythroid and myeloid precursors in bone marrow and also in monocytes, megakaryocytes, fibroblasts, endothelial cells, osteoblasts, and glial cells.²⁷ There is compelling evidence for the role of PDGF signaling in gastrointestinal stromal tumor (GIST), gliomas, chronic myelomonocytic leukemia, and nonmelanoma skin cancer.²⁸⁻³⁰ Overexpression of PDGFs and their receptors has been also reported in many other types of cancers such as prostate, ovarian, and non-small-cell lung cancer (NSCLC).^{31,32} Although it is not a general phenomenon, recent studies have demonstrated that PDGFs and their receptors are involved in human cancers through autocrine stimulation of tumor cell growth.³³

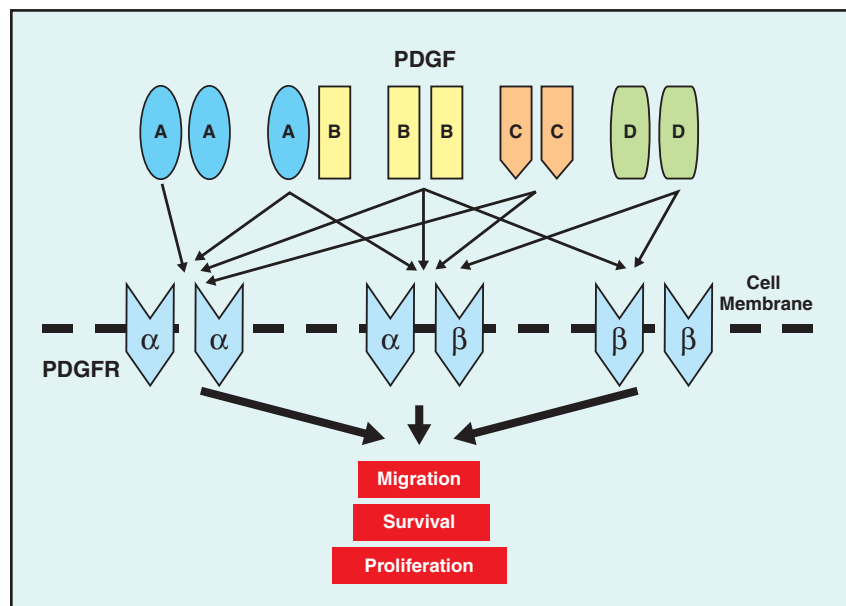


Fig 2. — PDGF and receptor interactions.

Development of angiogenesis and control of tumor interstitial pressure are suggested as PDGF mechanisms in tumor development.^{34,35}

VEGF and/or PDGF Inhibitors

Bevacizumab

Bevacizumab (BV) is a recombinant humanized monoclonal antibody (93% human and 7% murine) directed against VEGF. It was approved by the US Food and Drug Administration (FDA) in the first-line treatment of metastatic colorectal cancer in combination with an intravenous (IV) 5-fluorouracil (5-FU)-based regimen in 2004. This approval has been recently extended to the second-line setting as well.

In metastatic colon cancer, a large randomized multicenter phase III study helped to establish the role of BV.³⁶ A total of 813 patients with previously untreated metastatic colorectal cancer received either irinotecan (125 mg/m²), 5-FU (500 mg/m²) and leucovorin (20 mg/m²) (IFL) once weekly for 4 weeks every 6 weeks, plus BV (5 mg/kg every 2 weeks) or placebo. The median survival and progression-free survival in the placebo group were 15.6 months and 6.2 months, respectively, compared with 20.3 months and 10.6 months in the BV group ($P < .001$). Leukopenia, diarrhea, and hypertension were higher in the BV group. An analysis including this trial and two others showed a median survival of 17.9 vs 14.6 months in favor of BV (HR = 0.741,

$P=0.008$).³⁷⁻³⁹ The median duration of progression-free survival was also higher (8.8 vs 5.6 months, HR = 0.63, $P<0.001$). In a randomized phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG), 828 patients with advanced metastatic colorectal cancer refractory to a prior fluoropyrimidine/irinotecan-containing regimen received oxaliplatin (85 mg/m² IV) with LV (200 mg/m² IV) and 5-FU (400 mg/m² bolus) followed by 5-FU (600 mg/m²) by continuous infusion for 22 hours (FOLFOX-4) every 2 weeks alone or with BV (10 mg/kg IV every 2 weeks).⁴⁰ The median overall survival was 12.5 months for the combination arm vs 10.7 months for the FOLFOX-4 arm ($P=0.0024$) with 26% relative risk reduction of death. Neuropathy and hypertension were higher in the BV arm. Combining BV (5 mg/kg given every other week) and cetuximab (400 mg/m² cetuximab loading dose, then 250 mg/m² weekly) with or without irinotecan was also effective in a study of 74 irinotecan refractory metastatic colorectal cancer patients.⁴¹ The response rate of cetuximab/irinotecan/BV was 38% (23% response rate reported from cetuximab/irinotecan).

In metastatic breast cancer, the activity of BV appears to be limited when used in combination with capecitabine given as second-line or later therapy but not when combined with paclitaxel as first-line therapy.^{42,43} A total of 715 eligible patients were randomized to paclitaxel (90 mg/m²) weekly for 3 weeks of a 4-week cycle with or without BV (10 mg/kg) every 2 weeks. Progression-free survival was 11.4 months compared with 6.1 months in favor of the combination (HR = .51, $P<0.0001$). The overall survival data of the trial remains premature, with only 275 events reported. Grade 3 and 4 neuropathy, hypertension, bleeding, and proteinuria were all higher in the BV group.

In advanced or metastatic NSCLC, 99 untreated patients were randomized to paclitaxel (200 mg/m²) plus carboplatin (AUC 6 mg/mL) every 3 weeks with or without BV (7.5 or 15 mg/kg).⁴⁴ The group with the higher BV dose had a higher response rate (31.5% vs 18.8%), longer median time to progression (7.4% vs 4.2%, $P=0.023$), and an increase in survival (17.7 vs 14.9 months, $P=0.63$) compared with the control arm. There was no difference between the low-dose BV and the control arm. The study lacks sufficient power to make any definitive conclusions regarding a possible relationship between dose and treatment effect. Grade 3 and 4 toxicities were similar to what was reported in previous studies except for 6 patients who had a life-threatening hemoptysis or hematemesis (4 fatal). All 6 patients had centrally located tumors. A subanalysis showed patients with nonsquamous cell histology to have an improved outcome and acceptable safety risks.

A randomized phase III ECOG trial using the same treatment arms in 878 nonsquamous advanced or metastatic lung cancer patients was recently presented.⁴⁵

The same chemotherapy dose and schedule from the previous study was used. BV was given at 15 mg/kg until progression of disease. The overall response rate was 27% vs 10% ($P<0.0001$) in favor of the BV arm. Overall survival at 24 months was significantly higher in patients treated with BV (22% vs 17%, HR = 0.77, $P=0.007$). Grade 3 and 4 neutropenia (24% vs 16%), hypertension (6% vs 1%), and hemorrhage including hemoptysis (4.5% vs 1%) were all significantly higher in the BV arm.

A randomized, double-blind, phase II trial compared placebo with BV at doses of 3 and 10 mg/kg every 2 weeks in 116 metastatic renal cancer patients.⁴⁶ Crossover from placebo to antibody treatment was allowed. A significant prolongation of the time to progression of disease in the high-dose BV group was reported compared with the placebo group (HR = 2.55, $P<0.001$). The probability of being progression-free at 8 months was 30%, 14%, and 5% for patients on high-dose BV, low-dose BV, and placebo, respectively, with no significant differences in overall survival.

Combining BV with other targeted agents seems to show more encouraging results. A response rate of 25% and a stable disease rate of 61% were reported after 8 weeks of treatment with BV at 10 mg/kg IV every 2 weeks and erlotinib 150 mg orally daily in 59 metastatic renal cell carcinoma patients.⁴⁷ The survival rate at 18 months was 60%, and treatment was generally well tolerated.

Some phase I and II studies that evaluated BV alone or in combination with chemotherapy reported encouraging efficacy and safety results in hepatocellular, ovarian, renal cell, and pancreatic cancers, as well as in melanoma and soft tissue sarcoma.⁴⁸⁻⁵³ However, on September 23, 2005, the enrollment into a multicenter, single-arm phase II study of BV in platinum-refractory ovarian cancer patients was discontinued due to a higher rate of gastrointestinal perforations (11%). It has been suggested that VEGF inhibition may prevent the maintenance of the normal bowel microvasculature and promote necrosis. It is difficult to distinguish the influence of abdominal carcinomatosis and BV therapy causing bowel perforation in patients with recurrent ovarian carcinoma. Incorporating BV earlier in the course of treatment for recurrent ovarian cancer needs to be considered. Further studies are needed to identify the population that would benefit the most from BV.

Imatinib (STI157)

Imatinib is an oral tyrosine kinase inhibitor that blocks the activity of the *bcr-abl* oncoprotein and the *c-kit* tyrosine kinase cell surface receptor. Imatinib is also an inhibitor of the PDGFR kinase. The FDA approved imatinib for chronic myeloid leukemia (CML) and GIST in 2001.

Imatinib (400 to 600 mg/day) was evaluated in more than 1,000 patients in three stages of CML: blast crisis, accelerated phase, and chronic phase disease resistant or intolerant to interferon-alpha.⁵⁴ Study end-

points were cytogenetic response and hematologic response rate. The cytogenetic response rate was 49% in the chronic phase disease. The hematologic response rate in the accelerated phase and blast crisis stages was 63% and 26%, respectively. The most common imatinib adverse events were nausea, vomiting, myalgia, edema, and diarrhea. Elevated liver enzymes and/or bilirubin were reported in less than 3%. In metastatic and/or unresectable GIST, 147 patients received 400 mg or 600 mg of imatinib daily.⁵⁵ The overall response rate for the combined study arms was 38%, with no difference between the two dose groups. The diverse events were similar to what was previously reported.

As a PDGFR kinase inhibitor, imatinib has been evaluated recently in different malignancies where PDGF has been implicated. Three partial responses and 5 cases with prolonged (>6 months) disease stabilization were reported in a recent phase II study of 51 recurrent glioblastoma patients treated with imatinib.⁵⁶ A higher response rate was reported when imatinib was combined with hydroxyurea in the same population (9% partial response and 42% stable disease).⁵⁷ Imatinib has also clinical activity against both localized and metastatic dermatofibrosarcoma protuberans (DFSP) with t(17;22) and aggressive fibromatosis (desmoid tumor).^{58,59} A 50% complete response rate was reported when used in DFSP and 16% partial response in aggressive fibromatosis. Finally, the combination of imatinib and docetaxel has been shown to be tolerable and active in androgen-independent prostate cancer.⁶⁰ A decline in PSA levels by 50% maintained for 8 weeks was observed in 24% of patients. The role of imatinib in modulating outcomes to docetaxel in this population is being tested in a randomized phase II trial. Numerous studies are underway in hematologic and solid malignancies to further establish the anti-tumor role of imatinib.

Sorafenib (BAY43-9006)

Sorafenib is an oral small molecule tyrosine kinase inhibitor of c-Raf, B-Raf, PDGFR and VEGFR. In 2005, the FDA approved sorafenib to treat adults with advanced renal cell carcinoma.

Two trials using sorafenib in advanced clear cell renal carcinoma were conducted in patients who had received one prior systemic therapy. The first trial was a randomized discontinuation of sorafenib to determine the effects on tumor growth in patients with stable disease.⁶¹ A total of 202 patients entered a 12-week induction phase with sorafenib 400 mg twice daily and were then randomized to sorafenib 400 mg twice daily or placebo. At 24 weeks, 50% of the patients in the sorafenib group were progression-free compared with 18% of the placebo-treated patients ($P=.0077$). Median progression-free survival was also greater with sorafenib (23 vs 6 weeks, $P=.0001$). The

second trial randomized 769 patients to receive sorafenib 400 mg twice daily or best supportive care.⁶² Median progression-free survival as assessed by independent review for the sorafenib arm was 24 weeks and 12 weeks for the supportive care arm ($P<.00001$). The 12-week progression-free rate was 79% for sorafenib vs 50% for placebo. Drug-related toxicities (all grades) included rash, hand-foot-skin reaction, fatigue, diarrhea, and hypertension. Follow-up is in progress to complete the overall survival endpoint. Phase I studies of sorafenib alone or in combination with chemotherapy have shown encouraging results in melanoma, pancreatic and ovarian cancers.⁶³⁻⁶⁵ Studies in Kaposi's sarcoma and in lung, prostate, and hepatocellular cancers are underway.

Sunitinib (SU11248)

Sunitinib is an oral tyrosine kinase inhibitor that targets the PDGF, VEGF, c-KIT and FLT-3 receptors.⁶⁶ Sunitinib was approved by the FDA in 2006 for the treatment of GIST and advanced renal cell carcinoma based on the studies described below.

In a phase III multicenter study, 312 patients with progression of GIST despite prior imatinib therapy were randomized to receive sunitinib 50 mg/day for 4 weeks in repeated 6-week cycles or placebo.⁶⁷ An interim analysis led to unblinding the study because of the strongly positive efficacy results of sunitinib, which improved time to progression more than 4-fold compared with placebo (median: 27.3 weeks vs 6.4 weeks, $P<.0001$). This was also associated significantly with greater estimated overall survival (HR = 0.491, $P=.007$). Sunitinib was well tolerated. Side effects included fatigue, diarrhea, nausea, sore mouth, and skin discoloration.

In metastatic renal cell cancer, 63 patients who progressed after cytokine therapy were treated with 50 mg/day of sunitinib for 4 weeks in repeated 6-week cycles.⁶⁸ Partial responses were achieved in 40% of patients, and 27% demonstrated stable disease lasting 3 months or more. Median time to progression was 8.7 months. Dosing was generally tolerated with manageable toxicities. Adverse effects were similar to those reported in GIST patients.

A second phase II study single-arm, multicenter clinical trial treated 106 patients with metastatic renal cell cancer with repeated 6-week cycles of sunitinib 50 mg daily for 4 consecutive weeks followed by 2 weeks off.⁶⁹ The objective response rate was 34% and the median progression-free survival was 8.3 months (95% confidence interval, 7.8-14.5 months). The most common adverse events were fatigue (28%) and diarrhea (20%). Neutropenia (42%), elevation of lipase (28%), and anemia (26%) were the most common laboratory abnormalities. The final results of phase III trials are expected in the near future.

Two phase II studies evaluated sunitinib in breast and neuroendocrine tumors. In metastatic breast cancer, the partial response rate was 17% in patients who received prior chemotherapy including an anthracycline and taxane.⁷⁰ In advanced neuroendocrine tumors, a partial response rate of 13.5% (islet cell type) and a stable disease rate of 92% (carcinoid) have been reported. Treatment with prior cytotoxic chemotherapy was allowed, and patients receiving octreotide were allowed to continue treatment while on study.⁷¹ Sunitinib is being evaluated in melanoma, lung, and prostate cancers.

Leflunomide (SU101)

Leflunomide blocked both PDGF and epidermal growth factor (EGF)-stimulated DNA synthesis by inhibiting the PDGF-stimulated tyrosine phosphorylation of PDGF receptors.⁷² It has significant anti-inflammatory effects and is currently in clinical use as a disease-modulating agent in the treatment of rheumatoid arthritis.⁷³ In patients with hormone-refractory prostate cancer, a 4-day IV loading dose of leflunomide at 400 mg/m² followed by 10 weekly infusions at 400 mg/m² showed a PSA decline of more than 50% from baseline in only 3 out of 39 patients. The most frequent adverse events were asthenia, nausea, anorexia, and anemia.⁷⁴ A randomized phase III trial comparing the efficacy of leflunomide with that of procarbazine in patients with recurrent glioblastoma multiforme has completed recruitment.

Midostaurin (PKC412)

Midostaurin inhibits the autophosphorylation of receptors for VEGF, PDGF, and c-KIT. It can directly inhibit tumor growth and has antiangiogenic effects. At a dose of 50 mg/day IV, midostaurin was safely added to cisplatin and gemcitabine in patients with advanced NSCLC.⁷⁵ A higher dose was tolerated (150 mg/day) when combined with a continuous infusion 5-FU in patients with solid malignancies.^{76,77} Minor responses were reported. The principal toxicities were nausea, vomiting, stomatitis, and fatigue. This agent is being evaluated in acute myelogenous leukemia (AML) and systemic mastocytosis.

Semaxanib (SU5416)

Semaxanib inhibits VEGFR2 and KIT receptor tyrosine kinases with minor activity against PDGFRs.⁷⁸ In advanced or metastatic soft tissue sarcomas at a dose of 145 mg/m² twice weekly, semaxanib was relatively well tolerated but did not demonstrate significant antitumor activity.⁷⁹ The most common toxicities were headache, thrombosis, fatigue, nausea, and abdominal pain. The drug is lipophilic, highly protein-bound, and needs to be formulated with Cremophor and administered intravenously. Because of the toxicity of drug administration,

the lack of efficacy in combination with chemotherapy in patients with metastatic colon cancer, and the promise of newer agents, the development of semaxanib was terminated.⁸⁰

Vatalanib (PTK787/ZK222584)

Vatalanib is an oral, low-molecular-weight competitive inhibitor of the VEGF receptors and also has effects against PDGFR and c-KIT at higher concentrations. In a large randomized, double-blinded, placebo-controlled phase III trial, 1,168 patients with previously untreated metastatic colorectal cancer received first-line chemotherapy with oxaliplatin/5-FU/leucovorin (FOLFOX4) and 1,250 mg of vatalanib daily, or FOLFOX4 and placebo (CONFIRM-1 trial).⁸¹ Investigator analysis of progression-free survival showed some benefit of vatalanib with FOLFOX4 (HR = .83, *P* = .0026). Central review analysis was not statistically significant. Exploratory analysis showed patients with high lactate dehydrogenase (LDH) experienced the greatest improvement in progression-free survival. Survival data are needed to fully assess these results. Grade 3 or 4 hypertension and dizziness and increased incidence of pulmonary embolus were reported as possible vatalanib side effects. Phase I trials of vatalanib alone or in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel) in AML, myelodysplastic syndrome (MDS), and glioblastoma multiforme, as well as in ovarian, pancreatic, and renal cell cancers showed vatalanib to be well tolerated with some activity in some of these malignancies.⁸²⁻⁸⁶ It is currently being evaluated in breast, lung, and prostate cancers and multiple myeloma.

AG013736

AG013736 is an oral antiangiogenesis agent with activity against receptor tyrosine kinases, including VEGFR-1, VEGFR-2, VEGFR-3, c-kit, and PDGFR- β .⁸⁷ In patients with AML and MDS, AG013736 grade 3 or 4 toxicities included hypertension, mucositis, and deep venous thrombosis. No objective responses occurred; 2 patients with MDS had stable disease. Adverse events in solid tumors included hypertension, hemoptysis, and stomatitis.⁸⁸ The response rate was better (8%) than the response rate reported in AML and MDS. In metastatic renal cell carcinoma, 52 cytokine refractory patients had an encouraging 40% partial response rate with a median follow-up of 1 year.⁸⁹ Only 6% discontinued due to adverse events. This agent is currently being evaluated in a randomized study in combination with gemcitabine in chemotherapy-naive advanced pancreatic cancer patients.

AZD2171

AZD2171 is a highly potent oral VEGFR-2 tyrosine kinase inhibitor. Phase I trials in patients with advanced cancers and liver metastases and those with

advanced prostate adenocarcinoma^{90,91} showed this once-daily agent's adverse events to be fatigue, nausea, vomiting, anorexia, and diarrhea. One patient with liver metastases had minor response, and 1 with prostate cancer had a decrease in PSA of >50%. A phase II/III randomized study of AZD2171 in combination with carboplatin and paclitaxel in NSCLC is underway. AZD2171 is also being evaluated in combination with FOLFOX in metastatic colon cancer and in combination with gefitinib in NSCLC and head and neck cancers.

CDP860

This agent is a humanized, pegylated di-FAB' molecule that binds to and inhibits PDGFR- β . In a study of patients with advanced ovarian or colorectal cancer, IV infusions of 25 mg/kg CDP860 were given on days 0 and 28.⁹² The study was stopped after 3 out of 8 patients developed ascites and/or pleural effusions and 7 developed clinically significant fluid accumulation with no effect of CDP860 on tumor growth.⁹²

CP547,632

CP547,632 is an adenosine triphosphate-competitive and reversible oral inhibitor of the VEGFR-2 tyrosine kinase that potently inhibits receptor phosphorylation in preclinical studies.⁹³ In a phase I trial in combination with carboplatin and paclitaxel in chemotherapy-naive advanced NSCLC, CP547,632 was well tolerated.⁹⁴ The most common treatment adverse events were diarrhea, fatigue, nausea, neuropathy, emesis, alopecia, dyspnea, and arthralgia/myalgia. An objective response rate of 20% was reported. A phase II study of CP547,632 in patients with recurrent or persistent ovarian cancer, primary peritoneal cancer, or fallopian tube cancer has recently finished recruitment.

CP673,451

CP673,451 is a potent oral inhibitor of PDGFR- β . In a phase I study in solid tumors, nonmaculopapular rash and dry mouth were reported as drug-related adverse events.⁹⁵ Six out of 22 patients had stable disease but no objective response was reported.

RPI.4610

RPI.4610 is a chemically stabilized ribozyme targeting VEGFR-1. In solid tumors, it was well tolerated alone or in combination with chemotherapy as daily subcutaneous dosing.^{96,97} Hematologic adverse events were reported when used with chemotherapy. One complete response (bladder cancer) and one partial (esophageal cancer) were reported when RPI.4610 was used with carboplatin and paclitaxel. Two patients (nasopharyngeal carcinoma and melanoma) showed minor responses when RPI.4610 was used alone. Daily subcutaneous RPI.4610 is being evaluated in renal cell carcinoma.

SU6668

SU6668 inhibits the tyrosine kinase activity of VEGFR-2, PDGF and fibroblast growth factor (FGF) receptors. Its preclinical antitumor activity has been documented in many tumors including ovarian, glioma, melanoma, lung, and colon.⁹⁸ A phase I trial in solid tumors showed a high rate of toxicity with no objective responses.⁹⁹⁻¹⁰¹ Thrombocytopenia, pericarditis, pleuritic chest pain, nausea, abdominal pain, fatigue, headache, constipation, diarrhea, and abnormal liver function tests were reported as treatment side effects. The development of this drug has been discontinued due to unacceptable toxicity.

VEGF Trap

VEGF Trap is a potent angiogenesis inhibitor that consists of portions of human VEGF receptor VEGFR1 and VEGFR2 extracellular domains fused to the Fc portion of human immunoglobulin γ . It binds to VEGF-A up to 1000-fold more tightly than monoclonal antibodies and inactivates all circulating and tissue VEGF-A isoforms plus placental growth factor. In phase I trials in solid tumors and lymphoma, fatigue, pain, proteinuria, and constipation were the most common adverse events.¹⁰² No response has been reported. A phase II study in patients with platinum- and erlotinib-resistant locally advanced or metastatic NSCLC is currently recruiting participants.

ZD6474

ZD6474 is an oral low-molecular-weight inhibitor of the kinase activities associated with VEGFR-2 and epidermal growth factor receptor (EGFR). Metastatic breast cancer patients who received prior treatment with an anthracycline and taxane did not have any objective response when given ZD6474.¹⁰³ Diarrhea, rash, and QT prolongation were reported. After encouraging results in patients with locally advanced or metastatic NSCLC in phase I trials, ZD6474 is being evaluated in two phase II randomized studies: as a first-line treatment in combination with carboplatin and paclitaxel and after failure of first-line platinum-based chemotherapy in combination with docetaxel.^{104,105} Results from the safety run-in phase showed that combining ZD6474 with chemotherapy was generally well tolerated, without mutually additive toxicity in both studies. The randomized component of the studies has been initiated and continues to recruit with the final results being expected in the near future. Studies of ZD6474 in progressive or recurrent glioma (phase II) and in NSCLC (phase III) are underway.

YM359445

YM359445, an orally VEGFR-2 tyrosine kinase inhibitor, has a greater antitumor activity against established tumors in preclinical studies compared with other VEGFR2 tyrosine kinase inhibitors.¹⁰⁶

Conclusions

Compelling preclinical data motivated clinical trials with these agents in cancer, both as single agents and in combination with chemotherapy. Angiogenic agents inhibiting the VEGF and PDGF pathways have shown promising clinical results in a short period of time. Targeting more than one pathway by combining different agents might increase the antitumor activity of these drugs. In designing clinical trials, priority should be given to drugs that target more than one pathway, while noting that any drug combination needs to be done with caution since many of these drugs share the same side effect profile. The side effects of antiangiogenic agents targeting these pathways are quite distinct from chemotherapy agents and also from EGFR inhibitors and HER-2 inhibitors. New strategies to monitor and treat these side effects are needed, and clinicians must be aware of these toxicities. Although it is not completely understood how chemotherapy and angiogenesis inhibitors should be combined, the combination of BV and chemotherapy has been significantly more effective than given as a single agent. It is unclear if this is tumor-type specific or agent specific.

The implementation of reliable radiologic and pathologic angiogenesis monitoring techniques is necessary to fully implement antiangiogenic therapies in cancer. Angiogenic monitoring might help determine the efficacy of such treatment. The value of measuring VEGF in the serum is controversial. The role of these agents in the adjuvant setting and in combination with radiation therapy needs to be explored. While it is clear that multiple molecular pathways are dysregulated in tumor growth and single-target inhibition can sometimes be insufficient to produce durable responses, there is optimism that cancer treatment will be improved by the addition of these agents to the therapeutic armamentarium.

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