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REVIEW

Anti-angiogenesis therapies: their potential in cancer management

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Abstract: Angiogenesis plays an important role in normal animal growth and development. This process is also vital for the growth of tumors. Angiogenesis inhibitors have a different mechanism of action to traditional chemotherapy agents and radiation therapy. The angiogenesis inhibitors can act synergistically with conventional treatments and tend to have non-overlapping toxicities. There are four drugs which have a proven role in treating cancer patients. Bevacizumab is a humanized monoclonal antibody that binds to and neutralizes vascular endothelial growth factor (VEGF). Sunitinib and sorafenib inhibit multiple tyrosine kinase receptors that are important for angiogenesis. Thalidomide inhibits the activity of basic fibroblast growth factor-2 (bFGF). The licensed indications and the supporting evidence are discussed. Other drugs are currently being tested in clinical trials and the most promising of these drugs are discussed. Aflibercept, also known as VEGF-trap, is a recombinant fusion protein that binds to circulating VEGF. The vascular disrupting agents act by targeting established blood vessels. These exciting new treatments have the potential to transform the management of cancer.

Keywords: angiogenesis, bevacizumab, tyrosine kinase inhibitors, thalidomide, aflibercept, vascular disrupting agents

Introduction

Angiogenesis is the process by which new blood vessels grow from existing vasculature. It is an essential part of embryonic development. Primitive vascular networks of endothelial cells undergo budding and branching before associating with vascular smooth muscle. This vasculature can then support its local tissues with nutrients and oxygen. This process continues in childhood where it is necessary for the growth of long bones. In adults, angiogenesis is called into play again in certain situations, eg, wound healing.

A tumor is unable to grow beyond 2 mm diameter without neoangiogenesis.[1] Tumor hypoxia leads to an "angiogenic switch" altering the balance between pro-angiogenic and anti-angiogenic factors in favor of angiogenesis. Hypoxia occurs as the tumor outgrows its existing vascular supply. Hypoxia-inducible factor-1 production leads to increased vascular endothelial growth factor (VEGF) transcription.[2] VEGF causes increased vessel permeability and endothelial cell migration and proliferation. Hypoxia can also lead to increased production of other pro-angiogenic molecules such as nitric oxide synthase, platelet-derived growth factor (PDGF), transforming growth factors alpha and beta, basic fibroblastic growth factor (bFGF), and a class of protein growth factors called the angiopoietins. VEGF is probably the most important of these factors.[3,4]

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VEGF (also known as VEGF-A) is one member of a supergene family of growth factors. The other members are VEGF-B, VEGF-C, VEGF-D, PDGF and placental growth factor (PlGF).

These pro-angiogenic growth factors bind to receptor tyrosine kinases (RTKs) on the cell surface. These include PDGF receptors (PDGFRα and PDGFRβ), VEGF receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase 3 (FLT3), colony stimulating factor receptor type 1 (CSF-1R) and the glial cell-line derived neurotrophic factor receptor RET.

Activation of the VEGF receptor leads to signaling via the Ras/Raf/MEK/ERK pathway. VEGFR activation can also trigger intracellular signaling by phosphorylating other proteins such as phospholipase C-γ (PLC-γ), focal adhesion kinase (FAK), p38 and phosphoinositide 3′-kinase (PI3K).

Receptor tyrosine kinase inhibitors compete with adenosine triphosphate (ATP) for the ATP-binding site of the catalytic domain of the tyrosine kinase. RTK inhibitors thereby prevent the intracellular signaling which leads to angiogenesis.

It is possible that VEGF inhibitors produce a paradoxical increase in tumor blood flow and oxygenation due to "normalization" – the selective elimination of poorly formed blood vessels.[5] This could lead to enhanced delivery of cytotoxic chemotherapy drugs to the tumor. Radiation therapy depends on tumor oxygenation[6,7] and it is possible that an increase in tumor oxygenation leads to synergism between radiation therapy and VEGF inhibitors.

Angiogenesis inhibitors have a different mechanism of action and tend to have non-overlapping toxicities with cytotoxic chemotherapy and radiation therapy. There is therefore a logical rationale for combining these treatments.

The tumor vasculature differs from normal blood vessels in several ways (Table 1). These differences are exploited by a group of drugs called vascular disrupting agents (VDAs).

The aim of this review is to provide a summary of the most important anti-angiogenesis cancer therapies with their current indications and potential future uses.

Table 1 Features of tumor vasculature compared to normal blood vessels[8]

Increased vessel tortuosity
Vessels thin walled and fragile
Increased interstitial pressure within tumor
Vessel marker immaturity
Increased vessel permeability
Variable flow rates
Lack of vascular smooth muscle
Constant remodeling

Bevacizumab

Bevacizumab was the first angiogenesis inhibitor to be developed and used in the clinic.

Bevacizumab is a humanized monoclonal antibody that inhibits angiogenesis by binding to VEGF. The binding of bevacizumab to VEGF prevents VEGF binding to its receptors on the surface of endothelial cells. Bevacizumab thereby prevents VEGF-induced increased vessel permeability and endothelial cell migration and proliferation.

Bevacizumab was first approved by the United States Food and Drug Administration (FDA) in February 2004 for patients with metastatic colorectal cancer and it has since been approved for use with other cancers. The development and FDA approval of this drug paved the way for other novel agents.

Colorectal cancer – palliative treatment

Metastatic colorectal cancer has been treated for many years with 5-fluorouracil (5-FU) and leucovorin (LV). The addition of oxaliplatin and irinotecan in recent years has further increased overall survival.

The landmark phase III study of bevacizumab by Hurwitz et al randomized 813 patients to irinotecan and 5-FU/LV with or without bevacizumab. These patients all had previously untreated metastatic colorectal cancer. The patients who received bevacizumab had a higher response rate (44.8% versus 34.8% without bevacizumab, $P = 0.004$), median progression-free survival (PFS) (10.6 months versus 6.2 months, hazard ratio [HR] 0.54, $P < 0.001$), and overall survival (20.3 months versus 15.6 months, HR 0.66, $P < 0.001$).[9]

The Eastern Co-operative Oncology Group (ECOG) E3200 phase III study examined the role of second-line chemotherapy with oxaliplatin, 5-FU and LV (FOLFOX4) in 825 patients who had previously received irinotecan-based chemotherapy without bevacizumab. The patients who received FOLFOX4 with bevacizumab had an improved median survival of 12.9 months compared to 10.8 months with FOLFOX4 alone ($P = 0.0011$). There was also an arm of the trial with bevacizumab alone but this was closed early due to poor overall response rates and PFS.[10]

The N016966 phase III trial evaluated the use of bevacizumab as first-line therapy with fluoropyrimidine (5-FU or capecitabine) and oxaliplatin-based chemotherapy in

1,401 patients. The addition of bevacizumab significantly improved PFS (9.4 months versus 8.0 months in the placebo group, $P = 0.0023$) and there was a trend towards improved overall survival (21.3 months versus 19.9 months, $P = 0.077$).[11]

There are currently no results from randomized trials to indicate whether bevacizumab should be continued with second-line chemotherapy after failure of first-line chemotherapy with bevacizumab. Retrospective, observational data from the BRiTE study suggest there may be improved survival with continuation of bevacizumab.[12]

Unfortunately, bevacizumab does not confer significant additional benefit with 5-FU/LV alone in the context of third-line chemotherapy. TRC-0301 was a phase II study which enrolled 350 patients who were refractory to oxaliplatin and irinotecan. All patients received bevacizumab with 5-FU/LV. The overall response rate by independent assessors was 1% (95% confidence interval [CI] 0% to 5.5%). The median PFS was 3.5 months and the median overall survival was 9.0 months.[13]

Colorectal cancer – adjuvant treatment

Interest is currently focused on the adjuvant setting. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 study compared modified FOLFOX6 (mFOLFOX6) with and without bevacizumab.[14] This study randomized 2672 patients with stage II (24.9%) or stage III carcinoma of the colon and had a median follow up of 36 months. The addition of bevacizumab did not improve 3 year disease-free survival (HR 0.89, 95% CI 0.76 to 1.04, $P = 0.15$). There was a statistically significant benefit in prolongation of disease-free survival during the 1 year that bevacizumab was administered but this benefit was transient.[15] It is possible that bevacizumab is acting differently in the context of microscopic disease. Bevacizumab may only have a cytostatic effect in this context.

Results are awaited from the AVANT study which is evaluating FOLFOX4 versus FOLFOX4 plus bevacizumab versus oxaliplatin with capecitabine (XELOX) plus bevacizumab.[16] ECOG E5202 is studying FOLFOX6 with and without bevacizumab. This trial continues to recruit patients. It is anticipated that the 3 year disease-free survival data will be available by April 2011.[17] QUASAR 2 is investigating capecitabine with and without bevacizumab. This trial should complete recruitment in March 2010 and report in December 2013.[18]

The FDA have approved the use of bevacizumab in combination with chemotherapy in the first-line and second-line treatment of metastatic colorectal cancer.[19]

Breast cancer – palliative treatment

Patients with human epidermal growth factor receptor-2 (HER-2) negative disease were the first breast cancer patients to be studied with bevacizumab.

The ECOG E2100 trial was a first-line therapy, open-label phase III trial that enrolled 722 patients with metastatic breast cancer. They were randomized to have paclitaxel with or without bevacizumab. The patients who received bevacizumab had a higher objective response rate (36.9% versus 21.2%, $P < 0.001$) and a greater median PFS (11.8 months versus 5.9 months, HR 0.60, $P < 0.001$). There was no significant difference in median overall survival (26.7 months versus 25.2 months, HR 0.88, $P = 0.16$).[20]

The AVADO phase III trial enrolled 736 women with locally recurrent or metastatic breast cancer to one of three groups. Patients were randomized to receive either bevacizumab 15 mg/kg, 7.5 mg/kg or placebo. Compared to the placebo group, the 7.5 mg/kg group had a PFS HR of 0.69 (95% CI 0.54 to 0.89) and a HR of 0.61 (95% CI 0.48 to 0.78) for the 15 mg/kg group. The median survival data are not available yet.[21]

The RIBBON-1 trial randomized 1,237 patients to have first-line chemotherapy for locally recurrent or metastatic breast cancer with bevacizumab or placebo and the physician's choice of chemotherapy. Compared to the placebo group, the PFS HR with bevacizumab was 0.688 (95% CI 0.564 to 0.840) in the capecitabine group and 0.644 (0.522 to 0.795) in the pooled taxane and anthracycline group.[22]

The addition of bevacizumab to third-line chemotherapy does not confer additional benefit. A phase III trial by Miller et al randomized 462 patients to receive capecitabine alone or in combination with bevacizumab. These patients had all previously received an anthracycline and a taxane. The response rate was higher with combination therapy (19.8% versus 9.1% with capecitabine alone, $P = 0.001$) but there was no significant difference in PFS (4.86 versus 4.17 months) or overall survival (15.1 versus 14.5 months).[23] It appears that patients with such refractory disease respond differently to those given bevacizumab earlier in the course of their disease. It is possible that patients with refractory disease have several different angiogenic pathways which are activated and it would require more than a single anti-angiogenic drug to overcome this.

The US FDA has approved the use of bevacizumab in the first-line treatment of HER-2 negative metastatic breast cancer.[19] This decision was controversial. Some physicians were concerned that there was no proven overall survival benefit. The FDA, however, justified its decision on the

following grounds. Progression-free survival (PFS) had already been used as the primary endpoint for the approval of chemotherapy and hormonal therapy for metastatic breast cancer patients. Only a small number of the existing randomized, phase III trials in metastatic breast cancer patients for established drugs had actually shown a survival benefit. Furthermore, first-line trials in metastatic breast cancer patients would need to enroll enough patients to observe 2000 deaths in order to demonstrate, with 80% power, an improvement of 3 months in overall survival.[24]

Breast cancer – adjuvant treatment

With the approval of bevacizumab for use in metastatic breast cancer patients, the next logical question is whether adjuvant breast cancer patients would benefit too.

The ECOG E2104 study was a phase II trial of bevacizumab in addition to dose dense doxorubicin and cyclophosphamide followed by paclitaxel in patients with lymph node positive breast cancer.[25] This study showed that bevacizumab can be safely incorporated into anthracycline-containing regimens without causing cardiac dysfunction.[26] This has led to the following studies.

The BEATRICE study is a phase III trial investigating standard adjuvant chemotherapy with or without bevacizumab for patients with hormone receptor and HER-2 receptor negative breast cancer. The standard chemotherapy can be anthracycline or taxane-based or a combination of both. This trial has not yet completed accrual.[27]

The NSABP BETH study is a phase III trial of patients with HER-2 positive, lymph node positive or high risk node negative breast cancer patients. The standard chemotherapy is taxane-based or a combination of a taxane and anthracycline sequentially. All patients receive trastuzumab with or without concurrent bevacizumab. This trial continues to accrue patients.[28]

Non-small cell lung cancer

It has been shown that bevacizumab is of benefit in selected patients with non-small cell lung cancer (NSCLC).

The ECOG E4599 study was a phase III trial involving 878 patients with previously untreated advanced NSCLC. Patients with squamous cell carcinoma, hemoptysis, brain metastases and those on therapeutic anticoagulation were excluded to reduce the risk of pulmonary or cerebral hemorrhage. The patients were treated with 6 cycles of carboplatin and paclitaxel chemotherapy with or without bevacizumab. The median PFS was 6.2 months in the bevacizumab arm versus 4.5 months with chemotherapy alone (HR 0.66, $P < 0.001$). The median overall survival was 12.3 months versus 10.3 months without bevacizumab (HR 0.79, $P = 0.003$). Unfortunately, there were more treatment-related deaths in the bevacizumab arm (15 patients) than in the chemotherapy alone arm (2 patients). These 15 deaths included 5 deaths from hemoptysis and 2 due to hematemesis.[29] There is therefore an improvement in overall survival but with an increased risk of treatment-related death. One must balance the risks against potential benefits when prescribing for this patient group.

The AVAiL study was a randomized phase III trial involving 1,043 patients with advanced NSCLC and ECOG performance status of 0 or 1. Patients received cisplatin and gemcitabine with placebo or low-dose bevacizumab or high-dose bevacizumab. Patients with squamous cell carcinoma, a history of hemoptysis or cerebral metastases were excluded. The median PFS was higher with low-dose bevacizumab (HR 0.75, $P = 0.003$) and high-dose bevacizumab (HR 0.82, $P = 0.03$) compared to placebo. The trial was not sufficiently powered to detect a difference between the two different doses. The incidence of grade 3 or greater toxicities were similar in all three arms of the trial.[30] The incidence of grade 3 pulmonary hemorrhage was 1.5% or less for all three arms despite 9% of patients receiving therapeutic anticoagulation. There was no difference in overall survival between the three groups with a median survival of 13.6, 13.4 and 13.1 months for the low-dose, high-dose and placebo arms, respectively.[31]

The FDA has approved the use of bevacizumab for the first-line treatment of advanced NSCLC.[19]

Glioblastoma multiforme

The AVF3708g study was a phase II trial of bevacizumab given as a single agent or in combination with irinotecan in 167 patients with recurrent glioblastoma multiforme. All patients had received prior treatment with temozolomide. The initial results show objective response rates of 20% with bevacizumab alone or 33% in combination with irinotecan. The 6-month PFS rates were 35% and 50%, respectively. The overall survival was 9.2 months and 8.7 months respectively. These are encouraging results for this group of patients with a relatively poor prognosis.[32]

The National Cancer Institute (NCI) 06-C-0064E study investigated single-agent bevacizumab in 56 patients with recurrent glioblastoma multiforme. They all had previous surgery, radiation therapy and temozolomide or other systemic therapy. The objective response rate was 19.6%. The 6-month PFS rate was 29%. The median overall survival was 31 weeks.[33]

The results of these two trials led to fast-track approval of bevacizumab for glioblastoma multiforme by the FDA.[19]

Metastatic renal cell carcinoma

The AVOREN (BO17705) trial was a phase III trial of interferon-α (IFN-α) -2a with or without bevacizumab in 649 patients with metastatic renal cell carcinoma. The median PFS was significantly longer in the group that received bevacizumab (10.2 months versus 5.4 without bevacizumab, HR 0.63, 95% CI 0.52 to 0.75, $P = 0.0001$). Increases in PFS were observed irrespective of risk group or whether reduced dose IFN-α was used. Deaths due to adverse events were similar in both groups. There were 3 deaths that may have been related to bevacizumab.[34]

The CALGB 90206 study was a phase III trial using IFN-α with and without bevacizumab in 732 patients with metastatic renal cell carcinoma. The initial results show that the median time to progression was 8.5 months with bevacizumab and 5.2 months with IFN-α alone (HR 0.71, 95% CI 0.61 to 0.83, $P < 0.0001$).[35]

The FDA has approved bevacizumab for use with IFN-α in metastatic renal cell carcinoma.[19]

Combination with radiation therapy

There is one completed phase II study examining the role of bevacizumab with radiation therapy. Bevacizumab was given with 5-FU and radiation therapy to 32 patients prior to surgery for locally advanced rectal cancer. The treatment was generally well tolerated – most toxicities were grade 1 or 2 although there were 7 patients with grade 3 diarrhea and 3 patients with grade 3 hypertension. The tumor regressed in all patients with a mean size of 5 cm (range 3 to 12 cm) to an ulcer or scar with a mean size of 2.4 cm (range 0.7 to 6 cm). Histologic examination revealed either no cancer cells or scattered cancer cells in a bed of fibrosis.[36]

There is a phase II study of patients having post-operative treatment of glioblastoma multiforme with radiation therapy and concurrent temozolomide and bevacizumab. Patients receive external beam radiation therapy of 60 Gy in 30 fractions. This is given with temozolomide and bevacizumab during and after radiation therapy. An interim report in 2007 on the first 10 patients showed that the toxicities were acceptable.[37] The authors are continuing this study and they aim to recruit a total of 70 patients. This treatment is now also being evaluated in two randomized phase III trials which continue to recruit patients.[38,39]

There are also a large number of phase II trials in progress evaluating bevacizumab with radiation therapy in a variety of tumor sites including cervical cancer, pancreatic cancer, prostate cancer, lung cancer and sarcomas.

Adverse effects

The overall safety profile of bevacizumab has been compiled from data on over 3,500 patients with various malignancies. The most serious adverse effects were gastrointestinal perforation, hemorrhage (with hemoptysis occurring more commonly in non-small cell lung cancer patients), and arterial thromboembolism.

The risk of gastrointestinal perforation is generally less than 1% but up to 2% in colorectal cancer patients. The risk of grade 3–5 hemorrhage ranged from 0.4% to 5% in studies with bevacizumab versus up to 2.9% in the control groups. The rate of arterial thromboembolism was up to 3.8% with bevacizumab compared to 1.7% in the study control groups. The most common adverse effects include hypertension (in up to 34% of patients) and proteinuria (up to 38%). Grade 4 hypertension only occurs in 1.0% of patients and grade 4 proteinuria is experienced by 1.4% of patients.[40]

Tyrosine kinase inhibitors

The tyrosine kinase inhibitors were the next class of drugs to be developed.

The small size of the RTK inhibitors allows them to enter cells whereas the much larger monoclonal antibodies can only bind to the cell surface. There are a number of tyrosine kinase inhibitors currently under development (Table 2).

Sorafenib first received approval for the treatment of patients with advanced renal cell cancer in December 2005. Shortly afterwards, in January 2006, sunitinib received FDA approval for the treatment of advanced renal cell cancer and gastrointestinal stromal tumors.

Sorafenib

Sorafenib is an oral multi-targeted tyrosine kinase inhibitor. It was originally developed as an inhibitor of Raf-1 which is vital for cell proliferation. Sorafenib is also an inhibitor of VEGFR2 and 3, PDGFR-β, FLT3 and KIT.[41]

Renal cell carcinoma

A phase II study of sorafenib in renal cell carcinoma has yielded promising results. This study recruited 202 patients with renal cell carcinoma. Of the 193 evaluable patients, 70% were progression-free at 12 weeks. These patients were randomized to receive sorafenib or placebo. The median PFS for patients after randomization was 23 weeks with sorafenib and 6 weeks with placebo ($P = 0.0001$).[42]

Table 2 Current phase III randomized controlled trials of VEGF tyrosine kinase inhibitors

Drug	Indication
Axitinib (AG-013736)	First-line or second-line therapy for metastatic renal cell cancer First-line therapy for locally advanced, unresectable or metastatic pancreatic cancer (in combination with gemcitabine)
BIBF 1120	First-line therapy for ovarian cancer (in combination with paclitaxel and carboplatin) Second-line therapy for advanced NSCLC (in combination with docetaxel) Second-line therapy for advanced NSCLC (in combination with pemetrexed)
Brivanib alaninate (BMS-540215)	Adjuvant treatment following trans-arterial chemo-embolization (TACE) for hepatocellular carcinoma First-line treatment of hepatocellular carcinoma Second-line treatment of hepatocellular carcinoma Following irinotecan and oxaliplatin for metastatic colorectal cancer (in combination with cetuximab)
Cediranib (AZD2171)	First-line treatment of metastatic colorectal cancer (in combination with oxaliplatin and a fluoropyrimidine) Recurrent glioblastoma (alone and in combination with lomustine) First-line therapy of advanced NSCLC Relapsed ovarian epithelial, fallopian tube or primary peritoneal cancer (in combination with carboplatin and paclitaxel)
Pazopanib (GW786034)	Ovarian, fallopian tube or primary peritoneal cancer (immediately after first-line chemotherapy) Relapsed or progressive inflammatory breast cancer (in combination with lapatinib) First-line therapy for locally advanced or metastatic renal cell carcinoma Relapsed or progressive metastatic soft tissue sarcoma Adjuvant therapy in stage I NSCLC
Motasenib (AMG 706)	Advanced NSCLC (in combination with paclitaxel and carboplatin)
Semaxinib (SU5416)	First-line therapy for metastatic colorectal cancer (in combination with leucovorin and 5-fluorouracil) First-line therapy for metastatic colorectal cancer (in combination with leucovorin, 5-fluorouracil and irinotecan)
Sorafenib (BAY 43-9006)	Multiple trials in hepatocellular carcinoma, renal cell cancer, melanoma, pancreatic cancer, NSCLC, differentiated thyroid cancer
Sunitinib (SU11248)	Multiple trials in renal cell carcinoma, GIST, breast cancer, pancreatic cancer, NSCLC, colorectal cancer
Vandetanib (AZD6474)	Second-line therapy for NSCLC (in combination with pemetrexed) Second-line therapy for NSCLC (in combination with docetaxel) Second-line therapy for NSCLC Following failure of EGFR TKI in NSCLC
Vatalanib (PTK787/ZK222584)	First-line therapy for metastatic colorectal cancer (in combination with leucovorin, 5-fluorouracil and oxaliplatin) Irinotecan-resistant metastatic colorectal cancer (in combination with leucovorin, 5-fluorouracil and oxaliplatin)

Notes: All data from clinicaltrials.gov, accessed December 13, 2009.
Abbreviations: EGFR, epidermal growth factor receptor; GIST, gastro-intestinal stromal tumor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

This was followed by the phase III multinational TARGET trial, which was a double-blind, placebo-controlled trial of sorafenib. This trial recruited 903 patients of low- and intermediate-risk clear cell renal carcinoma. These patients had failed previous cytokine therapy. The primary endpoint was overall survival. The median PFS was 5.5 months in the sorafenib group and 2.8 months in the placebo group (HR 0.44, $P < 0.01$). Following the interim analysis, patients on placebo were allowed to crossover to receive sorafenib. An interim analysis of overall survival showed that sorafenib reduced the risk of death, as compared with placebo (HR 0.72, $P = 0.02$).[43] The final analysis of this data was presented at the American Society of Clinical Oncology (ASCO) 2007 meeting. It showed that patients treated with sorafenib had a median survival of 17.8 months versus 15.2 months with placebo. Although this was not statistically significant, the crossover of patients from placebo to sorafenib may have decreased the magnitude of the difference between the two groups. Response rates were lower than expected with partial responses reported in 10% of patients receiving sorafenib, while 78% showed stable disease.[44]

The FDA has approved the use of sorafenib in advanced renal cell carcinoma based on this data.[45]

Hepatocellular carcinoma

In the phase III SHARP trial, sorafenib was compared to placebo in 602 patients with biopsy-proven hepatocellular carcinoma. The median overall survival was 10.7 months in the sorafenib group versus 7.9 months for the placebo group (HR 0.69, $P < 0.001$). In addition, the median time to progression was in favor of sorafenib at 5.5 months versus 2.8 months in the placebo group ($P < 0.001$).[46]

On the basis of these data, the FDA has approved the use of sorafenib in patients with unresectable hepatocellular carcinoma.[45]

Adverse effects

In phase III studies, sorafenib caused diarrhea in 38% to 39% of patients compared to 9% of patients receiving placebo. Hand-foot syndrome occurred in 18%–19% of patients compared to 2% to 3% of patients taking placebo. Alopecia, anorexia and weight loss were also more common with sorafenib. There were relatively few grade 3 or 4 adverse effects. The only grade 3 adverse effects with sorafenib that occurred in more than 5% of patients were diarrhea (2% to 8%) and hand-foot syndrome (4% to 7%). Grade 4 toxicities were reported in less than 1% of patients.[47]

Sunitinib

Sunitinib is an orally bioavailable agent that inhibits multiple RTKs. Sunitinib has been identified as an inhibitor of various RTKs including PDGFRα, PDGFRβ, VEGFR1, VEGFR2, VEGFR3, KIT, FLT3, CSF-1R and RET.[48]

Renal cell carcinoma

Two phase II clinical trials have evaluated the role of sunitinib in patients with renal cell carcinoma (RCC).

In the first study, 63 patients with advanced RCC who had failed first-line cytokine therapy were enrolled. The majority had clear cell carcinoma. The response rate was 40% and the duration of response was 8.7 months.[49] The second study recruited 106 patients. They all had clear cell carcinoma and had failed previous cytokine treatment. There was a 34% partial response rate and the median PFS was 8.3 months.[50] In the pooled results from these two studies, the partial response rate was 42%. The median PFS in the combined analysis was 8.2 months. In the patients who had a complete or partial response, the median PFS was 14.8 months. In patients with stable disease for 3 months of more, the median PFS was 7.9 months.[51]

A randomized phase III trial compared sunitinib to IFN-α in the first-line treatment of patients with metastatic clear cell RCC. There were 375 patients in each arm of the trial. The median PFS for sunitinib was 11 months versus 5 months for IFN (HR 0.42, $P < 0.001$). The response rate in the sunitinib arm was 31% versus 6% for IFN. Median overall survival had not been reached in either treatment arm at the time of the interim data analysis. The median overall survival was 26.4 months in the sunitinib arm and 21.8 months in the IFN-α arm (HR 0.821, 95% CI 0.673 to 1.001, $P = 0.051$). Crossover to the sunitinib arm was allowed which might have decreased the magnitude of the difference observed.[52]

The FDA has approved the use of sunitinib in the first-line management of renal cell carcinoma.[53]

The role of sunitinib is being evaluated in the adjuvant setting in the Sunitinib treatment of Renal Adjuvant Cancer (S-TRAC) trial.[54] Sunitinib is also being evaluated in the Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Cell Carcinoma (ASSURE) trial.[55]

Gastro-intestinal stromal tumors

Patients with unresectable and metastatic gastro-intestinal stromal tumors (GISTs) have an improved PFS and overall survival when they are treated with imatinib.[56] Imatinib is an oral tyrosine kinase receptor inhibitor whose mechanism of action is not inhibition of angiogenesis – it acts mainly by inhibiting the activity of the fusion protein bcr-abl. GISTs exhibit KIT mutations in exons 9, 11 or 13 in 85% of tumors and 5% have mutations in PDGFRα.[57,58] Unfortunately, 20% of patients demonstrate primary resistance to imatinib and secondary resistance occurs in patients after a year of treatment, characterized by mutations in KIT and PDGFRα kinases.[59] In these patients, there were no effective therapeutic options until the use of sunitinib was investigated.[60]

A phase III trial enrolled 312 patients who were resistant or intolerant to imatinib and randomized them to receive either sunitinib or placebo. The PFS for patients treated with sunitinib was 24.1 weeks compared to 6.4 weeks for patients in the placebo group (HR 0.33, $P < 0.0001$). At the time of the initial analysis, more than half of the patients were still alive. The estimated median overall survival was better in the sunitinib group (HR 0.49, 95% CI 0.29 to 0.83).[60] Patients in the placebo group were allowed to crossover to sunitinib after the trial was unblinded. The median overall survival from an updated analysis presented at the ASCO 2008 meeting did not show a clear survival benefit (HR 0.82, 95% CI not stated, $P = 0.128$). A statistical analysis, which tries to take into account the effect of the crossover, suggests there would have been a survival benefit (HR 0.46, $P < 0.0001$) if the crossover had not been permitted.[61]

Adverse effects

The main side effects of sunitinib in phase II studies were fatigue, hypertension, nausea, diarrhea and mucositis. Hypothyroidism was also recorded.[49,50]

Grade 3 or 4 hypertension, diarrhea, hand-foot syndrome, nausea, vomiting, mucositis, and bleeding were more common with sunitinib than with IFN-α. The grade 3 or 4 laboratory abnormalities that were common with sunitinib were neutropenia, thrombocytopenia, leucopenia, increased lipase, increased amylase, hyponatremia, hyperuricemia, and hyperbilirubinemia.[52]

The adverse effects of the TKIs can be divided into "on-target" and "off-target". The on-target adverse effects are those that would be expected from their mechanism of action and include hypertension, proteinuria and hemorrhage. The off-target adverse effects include fatigue, diarrhea and nausea. The off-target effects are postulated to be due to the effects of TKIs on other kinases, complications from the patient's cancer and other illnesses.[62]

Thalidomide

Thalidomide was the most recent angiogenesis inhibitor to be approved by the FDA.

Thalidomide is a potent angiogenesis inhibitor. The use of this drug had been limited as it was withdrawn from the market due to teratogenicity but, in recent years, there has been a renewed interest in the use of thalidomide as an antitumor agent.

Thalidomide inhibits the activity of basic fibroblast growth factor-2 (bFGF). This peptide has an effect on endothelial cells by interacting with heparan-sulfate proteoglycans and tyrosine kinase FGF receptors. Thalidomide thereby inhibits angiogenesis.[63–65] Thalidomide may also have other antitumor properties such as inhibition of tumor necrosis factor alpha and alteration of expression of endothelial cellular adhesion molecules.[66,67]

There have been several studies testing the role of thalidomide in solid tumors. These have all shown disappointing results. The reasons for this are unclear. The main indication for thalidomide therapy is in the treatment of patients with myeloma. In May 2006, the FDA approved its use with dexamethasone for the treatment of patients newly diagnosed with multiple myeloma.

Combination with dexamethasone

In patients with myeloma, trials have shown that chemotherapy followed by stem cell transplantation provides the best overall survival for suitable patients.[68,69] Thalidomide with dexamethasone is now accepted as an effective induction therapy for newly diagnosed myeloma patients who are suitable for stem cell transplantation.

An ECOG phase III study compared thalidomide plus dexamethasone versus dexamethasone alone in 207 patients with newly diagnosed myeloma. The response rate with thalidomide and dexamethasone was 63% compared to 41% for the patients who received only dexamethasone ($P = 0.0017$).[70]

A further phase III study made the same comparison in 470 newly diagnosed myeloma patients. The response rate with thalidomide and dexamethasone was 63% compared to 46% with dexamethasone alone. The median time to progression was significantly better in the group that received thalidomide (22.6 versus 6.5 months, $P < 0.001$).[71]

A case-control study compared thalidomide and dexamethasone versus vincristine, doxorubicin and dexamethasone (VAD) as induction therapy prior to autologous peripheral blood stem cell transplantation. Thalidomide and dexamethasone produced a higher response rate than VAD (76% versus 52%, $P < 0.001$). There was also a greater reduction in myeloma cell mass of immunoglobulin G (IgG) and immunoglobulin A (IgA) types with thalidomide and dexamethasone.[72]

Combination with cytotoxic chemotherapy

In elderly patients with myeloma who are unsuitable for a stem cell transplant, the standard of care for several decades has been oral melphalan and prednisone.[73]

There have been three published randomized, controlled phase III trials comparing melphalan and prednisone with or without thalidomide.

In a study by the Italian Multiple Myeloma Network, 255 patients aged 60 to 85 were randomized to have melphalan and prednisone with or without thalidomide. The combined complete or partial response rates for patients who received thalidomide was 76.0% compared to 47.6% for patients who received only melphalan and prednisone (absolute difference 28.3%, 95% CI 16.5% to 39.1%). The data do not currently show a survival benefit. The 3-year survival rates were 80% for patients receiving thalidomide and 64% without thalidomide (HR 0.68, 95% CI 0.38 to 1.22).[73]

A trial by the Intergroupe Francophone du Myélome (IFM) randomized 321 patients aged 65 to 75 into three groups. There was a significantly better overall survival in the group with melphalan, prednisone and thalidomide. Their median overall survival was 51.6 months compared to 33.2 months for melphalan and prednisone alone (HR 0.59, 95% CI 0.46 to 0.81) and 38.3 months for patients who had a reduced-intensity autologous stem cell transplant (HR 0.69, 95% CI 0.49 to 0.96).[74]

The subsequent IFM 01/01 trial randomized 232 patients over 75 years old with newly diagnosed myeloma to having melphalan and prednisone with or without thalidomide. Median overall survival was significantly better in the group that received thalidomide (44.0 versus 29.1 months, $P = 0.001$).[75]

These trials have established the role for thalidomide with melphalan and prednisone as the standard of care for patients unsuitable for stem cell transplantation.

Adverse effects

The risk of severe teratogenicity and intra-uterine death with thalidomide is relatively high.[76] In the United States, thalidomide can only be dispensed as part of the System for Thalidomide Education and Prescribing Safety (STEPS) program.[77]

An increased risk of venous thromboembolism (VTE) has been observed. Interestingly, when used as a single agent, there is no increase in the risk of VTE with thalidomide.[78] When thalidomide is combined with dexamethasone, then the risk of VTE ranges from 12% to 26% compared to 3% with dexamethasone alone.[70,78,79] The risk of VTE is also high when thalidomide is combined with chemotherapy. In a study by Zangari et al, 100 patients were divided into 2 groups with comparable myeloma prognostic factors and VTE risk factors. They were randomized to receive different combinations of dexamethasone, vincristine, doxorubicin, cyclophosphamide, etoposide, and cisplatin with or without thalidomide. The patients who received thalidomide had a 28% VTE rate compared to 4% in the group who did not take thalidomide.[80]

Even in patients who do not have myeloma, the risk of VTE is significantly raised. For example, in a study of 47 prostate cancer patients receiving docetaxel chemotherapy with or without thalidomide, 9 out of 47 patients (19%) receiving thalidomide developed VTE whilst none of the 23 patients who received docetaxel alone developed VTE.[81]

Thalidomide also commonly causes the following adverse affects in at least 10% of patients – neutropenia, leucopenia, lymphopenia, anemia, thrombocytopenia, peripheral neuropathy, tremor, dizziness, paresthesia, dysesthesia, somnolence, constipation and peripheral edema.[76]

Thalidomide was the most recent angiogenesis inhibitor to be approved by the FDA but there are other drugs which are being developed for cancer patients. Following the development of the first angiogenesis inhibitor, bevacizumab, other drugs have been designed in the laboratory to inhibit VEGF.

Aflibercept

Soluble VEGF receptors are a relatively new group of drugs. These drugs use decoy soluble receptors to bind VEGF and thereby prevent VEGF binding to its receptors. Aflibercept (AVE0005, VEGF-trap) is the most promising member of this group. It has the highest affinity for VEGF of any of the soluble VEGF receptors and aflibercept-mediated blockade may be superior to that seen with the monoclonal antibody bevacizumab.[82] It is a fully humanized, recombinant fusion protein. Aflibercept contains immunoglobulin (Ig) domains from VEGFR1 and VEGFR2 fused to the Fc segment of IgG1. Aflibercept has a high affinity for VEGF-A, VEGF-B and placental growth factor. Binding of these molecules to aflibercept prevents them binding to their normal target receptors and thereby suppresses angiogenesis. Aflibercept is currently being tested in phase III trials.

Combination with cytotoxic chemotherapy

The majority of trials with aflibercept consist of single agent phase I and II studies and most of the phase II studies are still in progress. There are, however, some randomized, controlled phase II and III trials evaluating aflibercept with chemotherapy.

The following trials are all currently recruiting patients.

The Southwest Oncology Group (SWOG) S0802 study is a phase II study comparing aflibercept with placebo combined with topotecan in patients with extensive stage small cell lung cancer who have previously been treated with platinum-based chemotherapy.[83]

VELOUR is a phase III study comparing aflibercept with placebo in combination with irinotecan and 5-FU in metastatic colorectal cancer patients having second-line chemotherapy.[84]

VITAL is a phase III study evaluating docetaxel with aflibercept or placebo in patients as second-line treatment for patients with locally advanced or metastatic non-small cell lung cancer.[85]

VENICE is a phase III study comparing aflibercept with placebo in combination with docetaxel and prednisone in patients with metastatic androgen independent prostate cancer.[86]

Adverse effects

Aflibercept is generally well tolerated. Toxicities that occur in more than 10% of patients are hypertension, headache, proteinuria, fatigue, dysphonia, bleeding (epistaxis and hemoptysis), anorexia, abdominal pain, nausea, diarrhea, constipation and arthralgia. Grade 3 to 4 hypertension occurs in more than 10% of patients; the remaining grade 3 to 4 toxicities occur in less than 10% of patients and include headache, asthenia, anorexia and arthralgia. Venous thromboembolism, bleeding and perforation occur in less than 1% of patients.[87]

The drugs discussed so far have all focused on inhibiting the growth of new blood vessels. The vascular disrupting agents act in a completely different manner and this final

category of angiogenesis inhibitors may be one of the most promising groups of drugs under development.

Vascular disrupting agents

The vascular disrupting agents (VDAs) can target established tumor blood vessels. They act by causing a change in shape of the endothelial cells in the tumor's vasculature causing vessel leakiness, thrombus, and increased interstitial pressure. They can also cause physical blockage of the blood vessel due to a combination of rouleaux formation and slowing of blood flow leading to increased viscosity.[88] This leads to ischemia and necrosis of most of the tumor but a peripheral rim of viable cells usually remains. This class of drugs should work best when combined with other anti-tumor treatments in order to eliminate the rim of viable tumor cells.

There are two main classes of VDAs.

The biological (ligand-directed) VDAs combine an endothelium-targeting molecule with a toxin or pro-coagulant (Table 3).

The small molecule VDAs comprise the flavonoids and the tubulin-binding agents. The flavonoids act in a number of ways including cytokine induction and induction of apoptosis in endothelial cells. The tubulin-binding agents cause depolymerization of microtubules and disorganization of actin and tubulin.

These agents are currently under development. The agent that is in the most advanced stages of clinical evaluation is combretastatin. This drug is discussed below. For further information on all the other VDAs, the reader is directed to reviews by Gaya and Rustin[90] and Lippert.[91]

Combretastatin

Combretastatin A4 was originally isolated from the bark of the African willow tree *Combretum caffrum*. Combretastatin A4 phosphate is a water-soluble prodrug that is converted by endogenous phosphatases to the active drug.

Table 3 Examples of biological vascular disrupting agents[89]

Agent	Mechanism of action
Anti-endoglin-ricin A	Antibody bound to a toxin
Anti-TES-23-neocarzinostatin	Antibody bound to a cytotoxic agent
Anti-VCAM-1-tissue factor	Antibody bound to tissue factor (induces intravascular thrombosis)
L19 scFv-IL-12	Antibody bound to a cytokine
L19 scFv-TNFα	Antibody bound to a cytokine
VEGF-gelonin	Growth factor bound to a plant toxin

Abbreviations: IL, interleukin; TES, tissue endothelium specific; TNF, tumor necrosis factor; scFv, single chain variable fragment; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

Combretastatin is a tubulin-binding agent. Animal studies show that tumor blood flow can drop by more than 95%, one hour after administration.[88] There is extensive necrosis and this effect is relatively selective for tumors.[92]

Phase I studies showed encouraging response rates in a variety of tumor types and one patient with anaplastic thyroid cancer experienced a complete response and has remained disease-free for 5 years.[93]

Combination with cytotoxic chemotherapy

There are interim reports from 4 phase I/II trials examining combretastatin with chemotherapy. Three of these trials were with a mixture of patients with refractory solid tumors. In one study, 4 out of 16 patients (25%) had stable disease with carboplatin and combretastatin.[94] In a study with 27 patients, 4 (15%) achieved a partial response and 17 (63%) had stable disease when treated with combretastatin and either carboplatin, paclitaxel, or a combination of both.[95] In a further study with 13 patients, 3 (23%) had a partial response and 6 (46%) had stable disease with carboplatin, paclitaxel and combretastatin.[96] The remaining study involved 23 patients with platinum-resistant ovarian cancer treated with carboplatin, paclitaxel and combretastatin. There were six patients (26%) with confirmed partial responses.[97]

Combination with bevacizumab

A study using a murine model of human clear cell renal carcinoma showed a significantly enhanced antitumor effect when bevacizumab and combretastatin were combined.[98] Results are awaited from a completed phase I study with this drug combination in patients with advanced solid tumors.[99] A randomized phase II study is currently examining carboplatin, paclitaxel and bevacizumab with or without combretastatin in chemotherapy naïve patients with non-small cell lung cancer.[100]

Combination with radiation therapy

There are reports of combretastatin significantly enhancing the effects of radiation in animal tumor models.[101–105] There is a study of eight patients with non-small cell lung cancer who were given combretastatin after the second of six fractions of palliative radiotherapy. There was a significant decrease in tumor blood flow and increase in vascular permeability at 4 hours and 72 hours after combretastatin administration.[106]

Adverse effects

The dose-limiting toxicity is reversible ataxia. Other effects include vasovagal syncope, motor neuropathy and ischemia in

previously irradiated bowel, tumor pain, dyspnea and cardiac ischemia.[107–109] Other drug-related toxicities are pain, lymphopenia, fatigue, anemia, diarrhea, hypertension, hypotension, vomiting, visual disturbance, and dyspnea.[109]

Although the VDAs are at an earlier stage of development than the other drugs discussed, they are the most exciting class of drugs. Unlike the other drugs discussed, they can target established tumor vasculature which provides them with a unique and promising potential role in treating cancer. They need to be combined with other therapies as, on their own, they leave a peripheral rim of viable tumor cells.

Conclusions

Anti-angiogenesis drugs have already proven their value in the management of a number of different cancers. These drugs have non-overlapping toxicities with other therapies and a synergistic action.

Bevacizumab, sorafenib, and sunitinib have all proven their use in randomized phase III trials in several different solid tumor types. These drugs have a proven role in the metastatic setting but may not be as effective in the adjuvant setting. There is some evidence to suggest that their effects may be transient in this patient group but the results of further studies are awaited.

Thalidomide has established itself as the standard of care in the treatment of myeloma but has had disappointing results in solid tumors. The reasons for this are unclear.

Aflibercept is a promising agent which may be more active than bevacizumab due to its higher affinity for VEGF. This drug therefore has the potential to treat the same tumor types as bevacizumab but more effectively.

The vascular disrupting agents are less developed than the other drugs in this review however they are potentially the most exciting and promising group. They have varied mechanisms of action but they all act by disrupting existing tumor vasculature. The other drugs described in this review only have the ability to inhibit the growth of new vasculature.

The results of further studies currently in progress may lead to the increasing use of anti-angiogenesis therapies as part of multi-modality therapy with acceptable toxicity.

Disclosures

The authors have no conflicts of interest to disclose.

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