Antiangiogenic Drugs in Oncology: A Focus on Drug Safety and the Elderly – A Mini-Review

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Key Words

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Abstract

Angiogenesis is essential for normal tissue and even more so for solid malignancies. At present, inhibition of tumor angiogenesis is a major focus of anticancer drug development. Bevacizumab, a humanized antibody against VEGF, was the first antiangiogenic agent to be approved for advanced non-small cell lung cancer, breast cancer and colorectal cancer. The most commonly observed adverse events are hypertension, proteinuria, bleeding and thrombosis. Sunitinib, a small molecule blocking intracellular VEGF, KIT, Flt3 and PDGF receptors, which regulate angiogenesis and cell growth, is approved for the treatment of advanced renal cell cancer (RCC) and malignant gastrointestinal stromal tumor. The most frequent adverse events include hand-foot syndrome, stomatitis, diarrhea, fatigue, hypothyroidism and hypertension. Sorafenib, an oral multikinase inhibitor, is approved for the second-line treatment of advanced RCC and upfront treatment of advanced hepatocellular carcinoma. Most common adverse events with sorafenib are dermatologic (hand-foot skin reaction, rash, desquamation), fatigue, diarrhea, nausea, hypothyroidism and hypertension. More recently, cardiovascular toxicity has increasingly been recognized as a potential adverse event associated with sunitinib and

sorafenib treatment. Elderly patients are at increased risk of thromboembolic events when receiving bevacizumab, and potentially for cardiac dysfunction when receiving sunitinib or sorafenib. The safety of antiangiogenic drugs is of special concern when taking these agents for longer-term adjuvant or maintenance treatment. Furthermore, newer investigational antiangiogenic drugs are briefly reviewed.

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Introduction

Tumor Angiogenesis

With tumor progression, oxygen delivery by diffusion becomes insufficient, and tumors become increasingly dependent on their own blood supply (angiogenic switch). Proangiogenic mediators of the tumor microenvironment potentially result in enhanced proliferation of endothelial cells, and the development of a poorly structured tumor vasculature. Presently, members of the VEGF family (VEGF-A, B, C, D, placental growth factor, PLGF) and their receptors (VEGFR-1, 2, 3) have been identified as regulators of angiogenesis, with VEGF-A (referred to hereafter as VEGF) and its receptor VEGFR-2 as the main players. Binding of VEGF to the transmembrane receptor on endothelial cells initiates a cascade of intracellular downstream reactions that are mainly mediated by MAP kinase and PI3K/Akt/mTOR (fig. 1). This

Fig. 1. Mechanism of action of some antiangiogenic drugs. Adapted from Rini [40] and Sonpavde and Hutson [25].

results in the expression of hypoxia-inducible factor-1 α (HIF-1 α), with subsequent induction of proangiogenic factors such as platelet-derived growth factor (PDGF), fibroblast growth factor, hepatocyte growth factor, granulocyte colony stimulation factor, transforming growth factor- β and angiopoietins.

Surrogate Markers for Response Evaluation

Antiangiogenic drugs have already been added to therapeutic algorithms in various (solid) tumor entities, nevertheless there is a need to optimize pretreatment selection of patients. Unfortunately, there are no tumor characteristics or molecular markers that help to identify patients who are particularly likely to benefit from antiangiogenic treatment. Accordingly, there is special interest in finding predictive markers for clinical use. Plasma VEGF is a promising marker [1], as are newer imaging tools such as dynamic contrast-enhanced magnetic resonance imaging, PET-CT and contrast media-enhanced ultrasound [2] to visualize altered blood flow following the administration of antiangiogenic drugs.

Individual Compounds

Bevacizumab

The humanized monoclonal antibody bevacizumab (Avastin[®]) is directed against VEGF, and was the first antiangiogenic agent to be approved for advanced non-small cell lung cancer (NSCLC) [3], breast cancer [4] and colorectal cancer (CRC) [5]. Without the neutralizing effect of bevacizumab, binding of VEGF to VEGFR causes ligand-dependent receptor dimerization and tyrosine kinase autophosphorylation, resulting in activation of intracellular signaling pathways (fig. 1). VEGF itself may contribute to tumor growth and progression through enhancement of microvascular permeability, promotion of angiogenesis (via activation of endothelial cells, alteration of endothelial cell proliferation, induction of enzymes/proteins important for endothelial cell migration and sprouting) and protection against apoptosis.

Bevacizumab-associated side effects are generally mild to moderate in severity, although there are specific, uncommon events that are more severe and potentially life-threatening. The most commonly observed adverse events are hypertension, proteinuria, bleeding and thrombosis,

which are generally mild to moderate and manageable [6]. To ensure that hypertension is identified and treated as early as possible, it is recommended that patients receiving bevacizumab have their blood pressure monitored at least every 2–3 weeks [6]. Furthermore, bevacizumab should not be initiated in patients with uncontrolled hypertension. Bevacizumab-related proteinuria is mostly asymptomatic and detected only through laboratory analysis. Nephrotic syndrome in patients receiving bevacizumab is very rare, and mainly encountered in patients with renal cell cancer (RCC) [6]. Nevertheless, monitoring of patients treated with bevacizumab for proteinuria is recommended [6]. Bevacizumab increases the risk of venous thromboembolism [7], and also the risk of arterial thromboembolic events (ATE) in CRC patients [8]. In patients aged >65 years with a history of ATE, the frequency of bevacizumab-associated ATE is markedly increased from 2 to 18%. Despite being at increased risk of ATE, patients aged >65 years benefit from bevacizumab treatment according to registry-based safety data [9]. Serious hemorrhagic complications have been observed in patients with NSCLC receiving bevacizumab [10], and patients with squamous cell lung cancer were most at risk of severe hemorrhage. Therefore, patients with centrally located squamous cell lung cancer should not receive bevacizumab, and those with congenital bleeding diathesis, acquired coagulopathy, or those receiving full-dose anticoagulation should receive bevacizumab only with great caution [6]. Gastrointestinal perforation in patients receiving bevacizumab is very rare, and often associated with certain risk factors, such as an intact primary tumor of the colon, acute diverticulitis, obstruction, tumor at the site of perforation, abdominal carcinomatosis or a history of abdominal radiation [6]. Accordingly, treating oncologists should monitor patients for signs of gastrointestinal perforation, especially in the presence of known risk factors. As VEGF plays an essential role in wound healing, postoperative complications might not come as a surprise and patients should wait roughly 6 weeks after the last dose of bevacizumab before undergoing elective major surgery, such as hepatic resection in CRC patients.

Bevacizumab in the Treatment of the Elderly Patient

When focusing on elderly patients with CRC, the incidence of hypertension was increased in those receiving bevacizumab in combination with irinotecan as compared to irinotecan monotherapy [5], but hypertension was manageable using standard antihypertensive drugs. In a large community-based analysis in patients with CRC (BRiTE) [9], the overall tolerability of bevacizumab was

similar in patients aged 65 years or older as compared to those younger than 65 years, and age was not a significant predictor of bevacizumab-associated adverse events. However, there are some accumulating data showing that the incidence of ATE is higher in patients aged >75 years [11]. In elderly patients with NSCLC, Ramalingam et al. [12] showed that the addition of bevacizumab to standard chemotherapy did not improve clinical outcome, but resulted in increased toxicity (neutropenia, bleeding, proteinuria) and treatment-related deaths as compared to patients younger than 70 years. Therefore, the thromboembolic risk profile of patients receiving bevacizumab has to be carefully estimated, especially in elderly patients.

Sunitinib

Sunitinib (Sutent®) is a small molecule able to block intracellular receptor tyrosine kinase (RTK), which has both direct anticancer and antiangiogenic activity. Sunitinib selectively targets VEGF, KIT, Flt3 and PDGF receptors, and the receptor encoded by the ret proto-oncogene (fig. 1). Sunitinib is approved for the treatment of advanced and/or metastatic RCC [13], and for unresectable and/or metastatic malignant gastrointestinal stromal tumor after failure of imatinib treatment due to resistance or intolerance [14]. The most frequent non-hematological adverse events include stomatitis, nausea, diarrhea, vomiting, fatigue, hypertension, hand-foot syndrome and dysgeusia [15]. The most frequent hematological adverse events are thrombocytopenia, leukocytopenia and neutropenia [15]. With the 50 mg/day for 4 of 6 weeks schedule, dose reduction for severe (grade 3 or 4) toxicity was necessary in almost 50% of the patients, with permanent discontinuation in 3.7% of the patients [15].

Sunitinib in the Treatment of the Elderly Patient

Female gender and higher patient age were predictors for severe toxicity in a prospective non-randomized study [15]. In patients receiving sunitinib treatment, laboratory monitoring should include thyroid-stimulating hormone, as hypothyroidism is found in 50–80% of patients receiving sunitinib in prospective clinical studies. Potential mechanisms of TKI-related hypothyroidism include inhibition of thyroid vascularization and atrophy of the gland, drug-induced thyroiditis, reduced synthesis of thyroid hormones, inhibition of the thyroidal iodine uptake and depletion of the thyroid's functional reserve. Whether hypothyroidism is mediated by inhibition of the VEGF pathway or other molecular pathways is unknown. Levothyroxine is the standard treatment for overt hypothyroidism [16].

More recently, cardiovascular toxicity has increasingly been recognized as a potential adverse event associated with sunitinib treatment [17, 18]. Sunitinib-associated heart failure was found in 2.7% of the patients, and cardiac dysfunction was not completely reversible in most patients, even after termination of sunitinib treatment [17]. Patients with preexisting coronary artery disease are at a markedly increased risk of sunitinib-associated heart failure, why the elderly patient might be at increased risk of sunitinib-associated cardiac toxicity. Finally, recent data suggest a hypoglycemic effect of oral multi-tyrosine kinase inhibitors, warranting blood glucose testing to avoid hypoglycemia especially in patients with diabetes mellitus receiving antidiabetic medication [19].

Sorafenib

Sorafenib (Nexavar®) is an oral multi-kinase inhibitor (VEGFR-1, 2, 3, PDGFR- β) that inhibits tumor growth by acting on the tumor cells and cells of the tumor vasculature. It also inhibits tumor cell proliferation by targeting the MAPK pathway at the level of Raf kinase [20] (fig. 1). Unantagonized, these proangiogenic RTKs signal through Raf/MEK/ERK to induce proliferation of vascular endothelial cells, which form new blood vessels. By signaling through Raf, these proangiogenic RTKs also promote the proliferation of pericytes, which stabilize the newly formed blood vessels.

Sorafenib is approved for the use in advanced RCC when anticancer treatment with interferon- α or interleukin-2 has failed or cannot be used [21], and in hepatocellular carcinoma (HCC) [22]. Confirmation of the clinical activity of sorafenib in patients with advanced RCC was provided by the subsequent phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET). In this study, patients with advanced RCC receiving continuous oral sorafenib had an improved clinical outcome with a strong trend towards a longer overall survival as compared to patients on placebo [21]. In treatment-naïve patients with advanced HCC, sorafenib significantly prolonged overall survival as compared to placebo [22]. Most common adverse events with sorafenib as monotherapy are dermatologic (hand-foot skin reaction and rash/desquamation), constitutional (fatigue), and gastrointestinal (diarrhea and nausea) [21], as well as hypertension in 43–75% of the patients [18, 19]. Most of these adverse events are mild to moderate in severity and resolve with appropriate medical intervention, dose reductions or interruptions. Similar to sunitinib, sorafenib has been associated with hypothyroidism in 30–70% of the patients [16], and thyroid function monitoring should be adopted accordingly.

Sorafenib in the Treatment of the Elderly Patient

Eisen et al. [23] performed a subset analysis of the TARGET trial, looking at drug safety in elderly (>65 years) patients. A similar frequency of sorafenib-associated adverse events was noted across age groups, such as for diarrhea and hand-foot syndrome. Grade 3 and 4 adverse events were also similar between patients younger than 65 years and in those older than 65 years [23]. Because the elderly patient is frequently affected by cardiovascular comorbidity, these patients should have careful cardiac monitoring and cardiac treatment at the first signs of myocardial damage when receiving sorafenib.

Pazopanib

Pazopanib (Votrient®) is a newer oral small molecule inhibitor of multiple RTKs, with selective inhibition of VEGFR-1, 2, 3, c-kit and PDGFR [24] (fig. 1). Downstream effects of pazopanib include cleavage of caspase-8 and poly-ADP-ribose polymerase, and it induces downregulation of the anti-apoptotic molecules survivin, cIAP1 and 2, and Mcl-1 [25]. In phase I and II clinical trials, pazopanib was generally well tolerated. The most common adverse events are summarized in table 1. Pazopanib alone caused promising responses in patients with RCC, NSCLC, soft tissue sarcoma and gynecological tumors [26]. It is currently being evaluated in several trials as a single agent and in combination with sunitinib (RCC) and lapatinib (inflammatory breast cancer) [24].

Cediranib

Cediranib (AZD2171; Recentin®) is a once-daily oral tyrosine kinase inhibitor targeting VEGFR-1, 2, 3, c-kit and PDGFR. Early clinical studies show cediranib to be well tolerated as a monotherapy at doses of 45 mg/day, with a toxicity profile consistent with those seen in other VEGF-targeting agents (table 1). At 45 mg daily doses, common adverse events include fatigue, hypertension, diarrhea, nausea and vomiting [27]. However, Japanese solid cancer patients are suggested to be more sensitive to cediranib, with a daily dose of 30 mg being the maximum tolerated dose in this patient group [28]. The ongoing HORIZON phase III study is testing cediranib or bevacizumab in combination with FOLFOX chemotherapy in patients with metastatic CRC [29].

Vandetanib

Vandetanib (ZD6474; Zactima®) is an orally available, multiple tyrosine-kinase inhibitor with activity against VEGFR-2, EGFR and RET kinases. Inhibition of these RTKs blocks multiple intracellular signaling pathways

Table 1. Antiangiogenic compounds

Compound	Targets	Main adverse events	Caution	Indication
Bevacizumab (Avastin®)	VEGF	<i>Common:</i> hypertension, proteinuria <i>Moderately frequent:</i> bleeding, arterial and venous thromboembolic events, hypophosphatemia, thrombocytopenia <i>Rare:</i> gastrointestinal perforation, nephrotic syndrome, cardiac dysfunction	Uncontrolled hypertension Coagulopathy or bleeding diathesis Full-dose anticoagulation Intact primary tumor of the colon Acute diverticulitis Abdominal carcinomatosis History of abdominal radiation	Adv. NSCLC Adv. CRC Adv. breast cancer Adv. RCC
Sunitinib (Sutent®)	Intracellular VEGFR, KIT, Flt3 and PDGFR	<i>Common:</i> hypertension, hypothyroidism, thrombocytopenia, neutropenia, dysgeusia <i>Moderately frequent:</i> stomatitis, nausea, diarrhea, fatigue, hand-foot syndrome <i>Rare:</i> proteinuria, congestive heart failure, QTc prolongation, torsades-de-point, pancreatitis, liver dysfunction	Uncontrolled hypertension Preexisting cardiac dysfunction Concurrent treatment with CYP-inducing/-inhibiting drugs Preexisting QTc prolongation	Adv. RCC GIST Investigational
Sorafenib (Nexavar®)	VEGFR-1, -2, -3, PDGFR-β, Raf kinase	<i>Common:</i> hypertension, hand-foot syndrome, skin rash/desquamation, fatigue, hypothyroidism, leukocytopenia, hypophosphatemia, diarrhea <i>Moderately frequent:</i> nausea, proteinuria <i>Rare:</i> cardiac dysfunction, bleeding, gastrointestinal perforation	Uncontrolled hypertension Preexisting cardiac dysfunction Concurrent treatment with CYP-inducing drugs Liver dysfunction	Adv. HCC Adv. RCC Investigational
Pazopanib (Votrient®)	VEGFR-1, -2, -3, c-kit and PDGFR	<i>Common:</i> nausea, hypertension, diarrhea, fatigue <i>Moderately frequent:</i> anorexia, vomiting, hair depigmentation, elevated liver enzymes, rash, leukocytopenia <i>Rare:</i> dyspnea, hyperkalemia	Uncontrolled hypertension	Adv. RCC Investigational
Cediranib (Recentin®)	VEGFR-1, -2, -3, c-kit and PDGFR	<i>Common:</i> hypertension, fatigue, diarrhea <i>Moderately frequent:</i> nausea, vomiting, proteinuria, hand-foot syndrome, anorexia <i>Rare:</i> central nervous system ischemia	Uncontrolled hypertension	Investigational
Vandetanib (Zactima®)	VEGFR-2, EGFR and RET kinases	<i>Common:</i> skin rash, diarrhea <i>Moderately frequent:</i> hypertension, diarrhea, QTc prolongation <i>Rare:</i> central nervous system ischemia	Uncontrolled hypertension Preexisting QTc prolongation	Thyroid cancer Investigational
Axitinib	VEGFR-1, -2 and -3	<i>Common:</i> hypertension, fatigue, diarrhea <i>Moderately frequent:</i> stomatitis, nausea, vomiting <i>Rare:</i> bleeding, thromboembolic events, proteinuria	Uncontrolled hypertension Coagulopathy Bleeding diathesis Full-dose anticoagulation	Investigational
Combretastatin A4 (CA4)	Endothelial tubulin	<i>Common:</i> hypertension, hypotension, tachycardia, bradycardia, nausea, fatigue <i>Moderately frequent:</i> visual disturbances, dyspnea <i>Rare:</i> bowel ischemia	Preexisting cardiac dysfunction	Investigational
ASA404 (vadimezan)	Endothelial DNA	<i>Common:</i> hypertension, hypotension, nausea, fatigue <i>Moderately frequent:</i> urinary incontinence, visual disturbances, anxiety, confusion, tremor <i>Rare:</i> left ventricular failure, QTc prolongation	Preexisting QTc prolongation Preexisting cardiac dysfunction	Investigational

Adv. = Advanced; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; RCC = renal cell cancer; GIST = gastrointestinal stromal tumor; HCC = hepatocellular cancer.

involved in tumor growth, progression and angiogenesis. The most common treatment-related adverse events in a phase I study were dose-related diarrhea and skin rash [30] (table 1). Vandetanib 300 mg/day as a single agent was compared with gefitinib in a randomized, double-blind study in patients with advanced NSCLC [31]. Two trials are actually investigating the efficacy of the addition of vandetanib to docetaxel (ZODIAC) and peme-

trexed (ZEAL) as 2nd-line treatment in patients with locally advanced or metastatic NSCLC [32]. Two further trials are evaluating the efficacy of vandetanib as a single agent in patients with advanced NSCLC resistant to chemotherapy and EGFR inhibitors (ZEPHYR), and in 2nd-line treatment against erlotinib (ZEST) [32]. Furthermore, vandetanib has been granted orphan drug status in the US and Europe for medullary thyroid cancer.

Axitinib

Axitinib is an oral multiple tyrosine kinase inhibitor, targeting VEGFR-1, 2 and 3, PDGFR- β and c-KIT. Axitinib is more than 10-fold less potent for inhibiting PDGFR- β and c-KIT as compared to VEGFR. Dose-limiting toxicities in phase I studies were comparable to other tyrosine kinase inhibitor-type antiangiogenic drugs [33, 34] (table 1).

Vascular-Disrupting Agents

Vascular-disrupting agents (VDAs) target the established tumor vasculature and cause acute and pronounced shutdown of blood vessels resulting in selective tumor necrosis. VDAs have been divided into two types, small molecules and ligand-directed agents, with the former in a more advanced stage of clinical development. Small molecule VDAs can be divided into tubulin-binding agents (e.g. combretastatin, AVE8062, ZD6126) and the flavonoids (e.g. ASA404). The tubulin-binding agents act by blocking endothelial tubulin, resulting in disruption of the endothelial cytoskeleton and conformational changes leading to loss of blood flow [35]. ASA404 (vadimezan) is an active analog of flavone acetic acid causing DNA damage to endothelial cells. In two phase I studies of weekly infusions of ASA404, reversible dose-limiting toxicities included urinary incontinence, visual disturbance (blurring, color disturbance and photophobia), anxiety, confusion, tremor and possible left ventricular failure [36]. Asymptomatic QTc prolongation was seen at high doses of ASA404. ASA404 activity and safety was assessed in untreated advanced NSCLC patients in combination with carboplatin and paclitaxel [37]. No pharmacokinetic interaction was found between ASA404 and chemotherapy, and no severe vascular adverse events (bleeding, pulmonary hemorrhage, hemoptysis, hypertension, proteinuria) were described. A special focus of clinical development is NSCLC, but the best clinical applications of VDAs have still to be determined.

Potentially Detrimental Effects of Antiangiogenic Drugs

While antiangiogenic drugs have found their way into treatment algorithms in various solid tumors, clinical responses are usually limited and not enduring when they are given as single agents. A remarkable exception is RCC, where sunitinib and sorafenib have substantial clinical benefit, even when drug resistance usually emerges over a short time. More recent preclinical research suggests that

targeting angiogenesis in cases with low tumor burden might be detrimental and promote tumor spreading [38]. These important observations strongly suggest that inhibition of angiogenesis can have opposing effects on tumor growth and metastatic spread, depending on tumor stage and treatment duration [38]. The fear that antiangiogenic drugs might prove deleterious when given in an adjuvant fashion to patients with solid tumors following potentially curative treatment has been eased somewhat by the results of the recent NSABP study C-08 on the use of adjuvant bevacizumab in patients with early-stage CRC [39]. In the latter study, bevacizumab did not worsen clinical outcome nor did it generate severe toxicity. Nevertheless it is necessary to carefully investigate the potential influence of antiangiogenic drugs on metastatic spread.

Conclusions

Without any doubt, sunitinib and sorafenib, two oral multi-kinase inhibitors that inhibit multiple angiogenesis-related molecular pathways, have revolutionized the treatment of advanced RCC [13, 21] and HCC [22]. Additionally, the humanized antibody bevacizumab has been approved in combination with chemotherapy for advanced CRC [5], breast cancer [4] and NSCLC [3]. However, the benefit from the addition of bevacizumab in late-stage solid malignancies is mostly transitory, resulting in eventual drug resistance, tumor growth or regrowth, and rapid vascular recovery when therapy is stopped [38]. Additionally, despite relatively good tolerability of antiangiogenic drugs in general, there is the potential for increased toxicity in the elderly patient, especially in the case of increased risk for thromboembolic and/or bleeding events.

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