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1. ABSTRACT

The number of VEGFR tyrosine kinase inhibitors (TKIs) used as an anti-cancer agent is rapidly increasing, but several issues in clinical practice remain to be elucidated. VEGFR TKIs are multikinase inhibitors that have additional targets such platelet-derived growth factor receptors, which may result in an increased efficacy as well as an increased toxicity. Efficacy in several cancers has been shown, but acquired resistance also occurs during treatment with this new class of drugs. Tumor response evaluation can be a challenge, because VEGFR TKIs can cause extensive tumor necrosis without a marked decrease in tumor size. Therefore, new response criteria and functional imaging techniques are required. In this review we will also focus on the specific toxicities and their management: hypertension, proteinuria, cardiac toxicity, fatigue, hypothyroidism, voice changes, gastrointestinal toxicity, cutaneous reactions, wound healing, hemorrhage and thromboembolic events, hematological toxicity and cerebral toxicity. Furthermore we will discuss some issues regarding the pharmacology and dosing of these drugs. This review may provide important information to clinicians who prescribe VEGFR TKIs to their patients.

2. INTRODUCTION

Angiogenesis, the formation of new blood vessels from the existing vasculature, is essential for tumor growth and metastasis formation. Angiogenesis is a multi-step process where endothelial cells proliferate and migrate in the direction of specific stimuli. This can only happen with a concurrent remodeling of the extracellular matrix (ECM). Finally, tube formation occurs resulting in new blood vessel loops, which have to be stabilized. Several stimulating and inhibitory growth factors regulate this complex process (1). A key stimulator of angiogenesis is vascular endothelial growth factor (VEGF), which induces proliferation, differentiation and migration of endothelial cells (2). In addition, VEGF has a pro-survival effect on endothelial cells of newly formed vessels (3) and it increases vascular permeability (4). Compared to normal vasculature, tumor-associated vasculature consists of large and leaky vessels and has a disorganized structure with high interstitial pressure (5).

VEGF (also referred to as VEGF-A), is a member of a broader family, which includes VEGF-B/-C/-D/-E, placental growth factor (PlGF)-1 and -2 (2). In

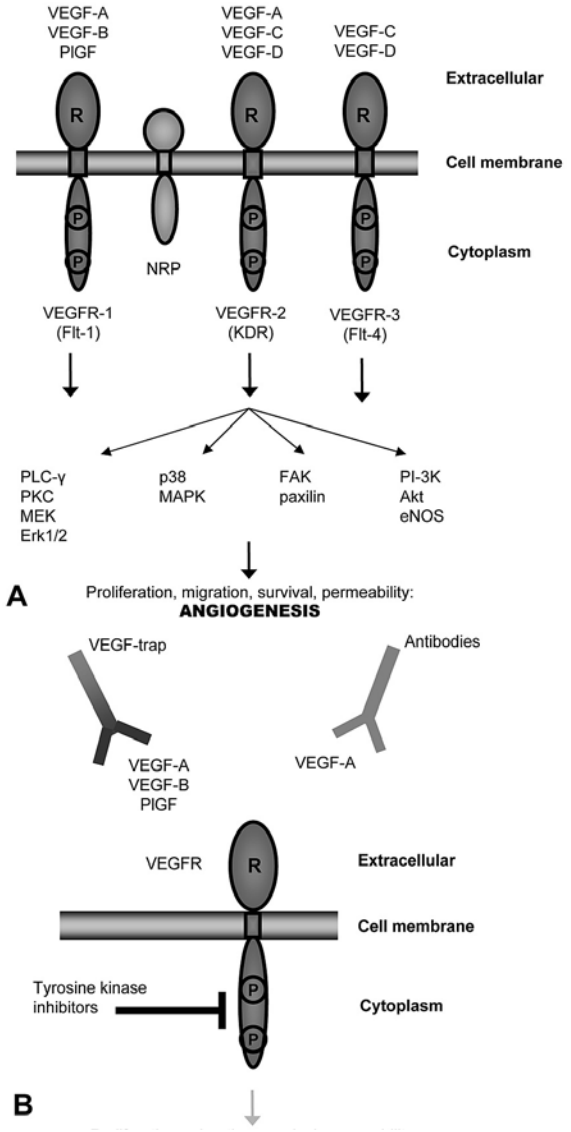

Figure 1. Schematic representation of the vascular endothelial growth factor receptors (VEGFR) on endothelial cells, VEGFR ligands and the intracellular signaling pathway leading to angiogenesis (a). Strategies to inhibit the VEGFR signaling pathways, leading to anti-angiogenic activity (b). For reasons of legibility only the most important molecules and connections are included in this figure. R, receptor (extracellular domain), P, phosphorylation site (intracellular domain), NRP, neuropilin

addition, alternative exon splicing generates four VEGF isoforms: VEGF121, VEGF165, VEGF189, VEGF206 (6), which all have different affinities for heparin binding. Acidic VEGF121 does not bind heparin and is secreted as a diffusible protein, whereas basic VEGF189 and VEGF206 bind heparin with high affinity and are sequestered in the ECM. VEGF165, the predominant isoform, can be secreted freely, but a considerable portion remains cell- or ECM-bound via heparan sulphate proteoglycans. Plasmin (7) and matrix metalloproteinase (MMP)-9 (8) can release the ECM-bound isoforms, creating the diffusible, bioactive fragment, VEGF110.

The production of VEGF by tumors is associated with tumoral hypoxia and genetic tumor aberrations, e.g. loss of tumor suppressors like p53, PTEN and Von Hippel Lindau (VHL) (9-11), and mutation or amplification of oncogenes (e.g. Ras) (12, 13). Growth factors like epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) can also induce VEGF expression (14, 15). Within tumors, the VEGF production of activated immune cells and fibroblasts may also be substantial (16, 17).

Members of the VEGF family exert their effects via three VEGF tyrosine kinase receptors VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4). VEGFR-1 and -2 are mostly expressed by vascular endothelial cells whereas VEGFR-3 is present on lymphatic endothelium. All VEGFRs are characterized by seven extracellular immunoglobulin-like domains, of which the second and third are critical for ligand binding, a transmembrane domain and a cytoplasmatic domain, which contains tyrosine kinase residues important for activating the intracellular signaling transduction pathway (Figure 1a). The ligands can form anti-parallel homodimers optimizing binding to their preferred receptor and facilitating receptor dimerization (18). The VEGF/VEGFR-2 complex seems to be the most important signaling route of activating endothelial cells. In addition, different affinity of the ligand for neuropilins, which are 130-kD transmembrane receptors expressed by a variety of cells including endothelial cells, can affect signal transduction (19). Neuropilin (NRP)-1 and -2 are no tyrosine kinase receptors, but they act as a co-receptor and potentiate the binding and activity of VEGF165 to VEGFR-2 (Figure 1a).

Other receptor tyrosine kinases and their ligands are also involved in angiogenesis: PDGF receptors (PDGFR), Tie receptors, fibroblast growth factor receptors (FGFR), hepatocyte growth factor receptors (HGFR) and ephrin receptors (EphR). Briefly, PDGFR and FGFR will be described, since some of the compounds discussed in this review inhibit these pathways. PDGFRs are composed of two chains (α or β) resulting in three distinct receptors (αα, αβ, or ββ). Some structurally related receptors, such as c-Kit and Fms-like tyrosine kinase (Flt3), belong to the same family as PDGFRs. The family of PDGF-ligands consists of four homodimers, PDGF-AA, -BB, -CC, and –DD, and the heterodimer PDGF-AB, which bind to α- and β-receptors with different specificities (20). PDGFR signaling is involved in blood vessel development and wound healing and is involved in maintaining interstitial fluid pressure. PDGF-B is expressed by endothelial cells while PDGFR-β is expressed by pericytes and smooth muscle cells covering the blood vessels, suggesting a role of PDGFR signaling in recruitment of perivascular structures (21). The family of FGFRs comprises 4 different receptors, which can bind more than 20 different heparin-binding FGFs with different affinity. FGF-1 and -2 induce

Table 1. IC_{50} (uM) of indicated receptors determined by kinase assay unless stated otherwise

Drug	Generic name	IC_{50} (uM)[1]									
		VEGFR1	VEGFR2	VEGFR3	PDGFRa	PDGFRb	Flt3	c-Kit	FGFR1	FGFR2	FGFR3
AEE788		0.059	0.077	0.330		0.320	0.720	0.790			
ABT869		0.003	0.004	0.190		0.066	0.004	0.014	>12.500	>12.500	>12.500
AG013736	axitinib	0.0001[2]	0.0002[2]	0.0003[2]	0.005[2]	0.002[2]	>1.000[2]	0.002[2]	0.231[2]		
AMG706		+	+	+	+	+		+			
AZD2171	cediranib	0.005	<0.001	<0.003	0.036	0.005	>1.000	0.002	0.026		
ZD6474	vandetanib	1.600	0.040	0.108		1.1		>20	3.6		
BAY 43-9006	sorafenib		0.090				0.058	0.068	0.580		
BAY 57-9352	telatinib		+	+		+		+			
BAY 73-4506	DAST		+	+	+	+		+			
BIBF1120		0.034	0.021	0.013	0.059	0.060			0.069		0.137
BMS 582664	brivanib alaninate	0.350	0.034	0.010					0.145	0.125	
CHIR258		0.010	0.013	0.008	0.200	0.027	0.001	0.002	0.008		0.009
CP-547,632			0.011			2.820					
E7080		+	+			+			+		
GW786034	pazopanib	+	+	+	+	+		+			
KRN951		0.030	0.007	0.015	0.040	0.049	> 1	0.078	0.530		> 1
PTK787	vatalanib	0.077	0.037	0.66		0.58		0.73			
SU011248	sunitinib		0.01[2]			0.01[2]	0.250[2]	0.01[2]			
SU014813		0.002	0.05		0.024[2]	0.004	0.012[2]	0.015	3.5		
XL647			+								
XL999			+		+	+	+		+		+

Drug	Generic name	IC_{50} (uM)[1]						T1/2 (h)	Phase	Ref
		Src	Raf/ BRAF	RET	EGFR	ErbB2	Tie2			
AEE788		0.061	2.8	0.740	0.002	0.006			I	
ABT869		>50.000		1.900	>50.000		0.170	17± 5	I	(2; 3)
AG013736	axitinib			>1.000[2]				2-5	II	(4-6)
AMG706								5-8	I	(7)
AZD2171	cediranib	0.13			1.600	>1		17-27	III[3]	(8; 9)
ZD6474	vandetanib				0.500	>20	2.5	90-134	III[3]	(10; 11)
BAY 43-9006	sorafenib		0.006	0.050[2]	> 10.000			24-38	REG (RCC)	(12-14)
BAY 57-9352	telatinib								I	(15)
BAY 73-4506	DAST		+	+					I	(16)
BIBF1120		0.156						7-24	II	(17; 18)
BMS 582664	brivanib alaninate								I	(19; 20)
CHIR258			>25.000		2.218	>20.000		10-17	I	(21; 22)
CP-547,632					6.250		0.048	29-32	I	(23; 24)
E7080									I	(25)
GW786034	pazopanib							26-46	II	(26)
KRN951		0.960			> 1	> 1	0.078		I	(27; 28)
PTK787	vatalanib							3-6	III	(29; 30)
SU011248	sunitinib	0.6		0.224[2]	> 10			41-86	REG (RCC, GIST), III[3]	(31-35)
SU014813		2.5			> 20				II	(36; 37)
XL647					+	+		50-70	I	(38)
XL999		+							II	(39)

[1] Biochemical IC_{50} (μM), values were determined in biochemical kinase assays using recombinant enzymes, [2] Cellular IC_{50} (μM), values were determined by measuring intrinsic or ligand-stimulated kinase activity (phosphorylation) in cell lines expressing a given target, [3] Clinical trials.gov, T1/2, half-life, Phase, most advanced phase of clinical testing, Reg, registered as standard anti-cancer treatment for indicated tumor type; RCC, renal cell carcinoma; GIST, gastrointestinal stroma tumor

endothelial cell proliferation, migration and protease production (22).

Although there is a redundancy of proangiogenic growth factors and their receptors, VEGF is supposed to be the most important factor sustaining angiogenesis. Proof-of-principle was provided by xenograft mouse models, in which neutralizing VEGF-antibodies or VEGFR interference inhibited tumor growth substantially and even induced tumor regression (23, 24). These early findings were confirmed and extended in a variety of animal models.

In mature tissues, angiogenesis occurs mainly during wound healing, in the female reproductive cycle and during ischemia. Therefore targeting tumor-associated angiogenesis represents a promising anti-cancer therapy with reduced toxicity in adults. Anti-angiogenic therapy affects mostly the immature, disorganized tumor vasculature leaving the remaining tumor vasculature to function better with a subsequent improved perfusion (5, 25). In glioblastoma patients, magnetic resonance imaging (MRI) established a rapid, but reversible, normalizing effect of the anti-angiogenic agent cediranib (AZD2171) on tumor vessels, resulting in a promising response rate. In addition, reduction in permeability correlated with a decrease of tumor-associated brain edema (26).

Bevacizumab, a monoclonal humanized antibody directed against VEGF, was the first anti-angiogenic agent to be registered (27). Inhibition of the VEGFR kinase activity is another strategy to inhibit the VEGFR pathway. This review focuses on VEGFR tyrosine kinase inhibitors (TKIs), which are low-molecular weight, ATP-mimetic proteins that bind to the intracellular site of the tyrosine kinase domain of VEGFRs, resulting in a blockade of the intracellular pathway (Figure 1b). The number of VEGFR TKIs in clinical trials is rapidly increasing and some are already registered (Table 1). In this review we address remaining questions regarding response evaluation, specific toxicities, dosing and scheduling of these agents, and rational combinations with other anti-cancer therapies.

3. EFFICACY

The VEGFR TKIs sunitinib (SU11248), sorafenib (BAY 43-9006) and axitinib (AG-013736) have demonstrated their efficacy in metastatic renal cell cancer (RCC). In a randomized phase III clinical trial sunitinib had an objective response rate of 31% which was significantly

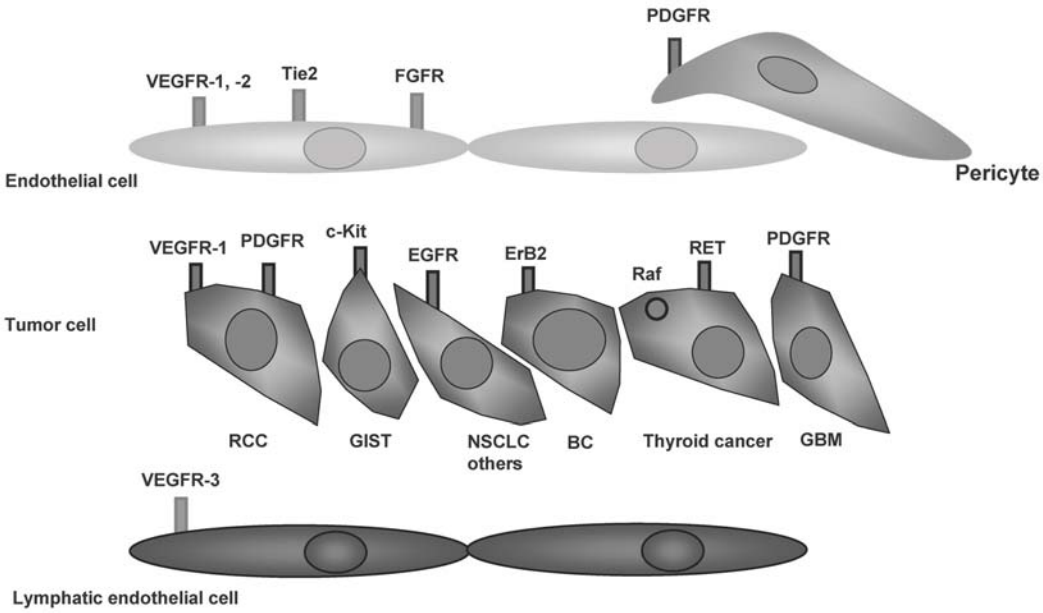

Figure 2. Additional targets of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors, which may contribute to their anti-tumor efficacy either by targeting tumor-associated vessels or by targeting the tumor cells themselves. RCC, renal cell cancer; GIST, gastrointestinal stromal tumor; BC, breast cancer; NSCLC, non-small cell lung cancer; GBM, glioblastoma multiforme

higher than the 6% in the interferon-alpha (IFN-α) group (28). The progression-free survival on sunitinib was 11 months, while that on IFN-α was 5 months (28). As compared with the placebo group, treatment with sorafenib prolonged the progression-free survival with almost 3 months in RCC patients, resistant to standard cytokine therapy (29), but failed to improve the progression-free survival in comparison to that of IFN-α as studied in the first-line setting (30). Recently, a phase II study has been reported demonstrating the efficacy of axitinib in cytokine-refractory RCC patients (31). The success of VEGFR TKIs in clear cell RCC can be explained by its tumor biology. Clear cell RCC is characterized by a defect in the VHL tumor suppressor gene leading to stabilization of the hypoxia-inducible factor (HIF)-1-α protein and subsequently to overexpression of VEGF and PDGF resulting in tumor progression and angiogenesis (32). Additional targeting of PDGFR by VEGFR TKIs might explain the higher response rate of VEGFR TKIs in RCC when compared to bevacizumab (33).

Efficacy data of VEGFR TKIs concerning other tumor types are still immature, but interesting response data in (early) clinical trials have been observed. For example, sunitinib in phase II clinical trials had promising activity in metastatic breast cancer (34) as well as advanced non-small-cell lung cancer (35). Sorafenib showed antitumor activity in prostate cancer (36-38) and improved overall survival with 44% in hepatocellular carcinoma patients when compared with placebo (39). Sorafenib and axitinib have shown objective response rates of 33% and 22% respectively in thyroid cancer (40, 41). In some settings, the inhibitory activity of VEGFR TKIs to receptors other than VEGFRs (Figure 2) may be responsible for their efficacy: inhibition of c-Kit by sunitinib may be responsible for its success in imatinib-resistant gastrointestinal stromal tumors (GIST) (42) and inhibition of Raf and RET by sorafenib may explain the clinical efficacy in thyroid cancer (40)(Figure 2).

In settings where chemotherapy is considered standard of care, VEGFR TKIs are being added to increase efficacy. VEGFR TKIs may improve the tumoral uptake of anticancer agents by a vessel normalization effect. In mice bearing glioma xenografts, sunitinib has demonstrated to increase the temozolomide tumor distribution (43). Most advanced data are available from phase III studies which investigated the potential benefit of adding vatalanib (PTK787/ZK 222584) to chemotherapy (FOLFOX 4) in colorectal patients (CONFIRM-1 and -2 (44, 45)). Although the results indicate that patients with high baseline serum lactate dehydrogenase levels benefit from vatalanib treatment, this did not increase survival in the whole population (46). A high drop-out rate in the vatalanib arm of the CONFIRM-1 study, due to toxicity, might have contributed to the unsatisfactory results. Furthermore, vatalanib administrated as a single daily dose might be less effective due to a short half life (i.e., ~ 6 hours). Bevacizumab, which has a longer half life (i.e., ~ 20 days) and is administered once in three weeks, did increase the efficacy of chemotherapy in colorectal cancer patients (27). VEGFR TKIs have also been combined with other targeted therapy such as bevacizumab (47, 48) and agents that target the EGF receptor (49-51) or the mammalian target of rapamycin (mTOR) (52), however, efficacy data are still incomplete. Two phase II studies combining sorafenib with IFN-α in RCC patients have recently been reported (53, 54). These studies suggested higher response rates for the

combination, however, toxicity also exceeded that of either agent alone.

Angiogenesis inhibitors might ultimately increase the radioresistance of tumor cells, by inducing more tumor hypoxia (55). However, preclinical studies have shown that anti-ngiogenic therapy can increase anti-tumor effects of radiotherapy (56-58). Preclinical data have suggested that angiogenic factors, like VEGF, being a survival factor for endothelial cells, are upregulated in tumors during radiotherapy (59, 60).

Even after an initial VEGFR TKI-induced regression, tumors eventually progress. Preclinical studies have demonstrated that this acquired resistance may be associated with upregulation of VEGF and other angiogenic factors (61, 62). Increased tumor hypoxia upon administration of VEGF(R) interfering agents has been demonstrated in preclinical models (63, 64) and this may, via stabilization of HIF-1α result in increased production of a variety of angiogenic factors, like HGF and FGF (61, 62).

4. RESPONSE EVALUATION

Most VEGFR TKI trials use the bi-dimensional World Health Organization (WHO) criteria or the uni-dimensional Response Evaluation Criteria in Solid Tumors (RECIST) (65). The RECIST criteria are most widely used and are based upon the sum of the longest diameters of the appointed target lesions in the transversal plane. Objective responses may be missed or underestimated by RECIST (66), since VEGFR TKIs can cause direct and rapid anti-vascular effects, leading to secondary tumor necrosis without a marked decrease in tumor size (66-68). Furthermore, tumor markers used for response monitoring during therapy with conventional agents may lack efficacy to monitor VEGFR TKI response, as it has been suggested for the prostate-specific antigen (PSA) in prostate cancer patients treated with sorafenib (36, 37) and CA125 in ovarian cancer patient treated with sorafenib (69). Choi response criteria have recently been defined to evaluate responses in GIST patients treated with imatinib (70, 71). In this setting, the Choi criteria correlated better with disease-specific survival than RECIST. According to these criteria a response is defined as a ≥10% decrease in one-dimensional tumor size or a ≥15% decrease in tumor density on computed tomography. The Choi response criteria may also be of value to evaluate tumor responses after treatment with VEGFR TKIs.

Instead of conventional morphologic imaging, functional imaging can be applied to measure the efficacy of VEGFR TKIs. Several vascular end-points such as tumor blood volume, tumor blood flow rate, perfused/non-perfused tumor fractions and vascular permeability-surface area can be determined by techniques such as Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI), Perfusion Computed Tomography (CTP), Dynamic Contrast Enhanced Ultrasound (DCE-US) and Positron Emission Tomography (PET) using different PET tracers (72). In only a few trials such techniques have been applied to evaluate the tumor response to VEGFR TKIs.

DCE-MRI has been used in assessing tumor vascularity and permeability following treatment with the agents sorafenib, vatalanib and axitinib (73-75). In sorafenib-treated RCC, DCE-MRI seemed to be a promising tool to predict progression-free survival (73). In colon cancer vatalanib caused a reduction in DCE-MRI contrast enhancement parameters within 26 to 33 hours of administration of the first dose (75), and in patients with advanced solid tumors an immediate decrease in tumor vascular parameters as measured by DCE-MRI was seen on day 2 after axitinib administration (74). A decrease in tumor perfusion has been demonstrated by CTP after administration of cediranib (76). In RCC patients treated with sorafenib an early reduction in tumor vascularization/tumor volume measured by DCE-US was shown to correlate with response and progression-free and overall survival (77, 78). The obvious advantage of DCE-US is that it is simpler, more patient-friendly and cheaper than the other imaging modalities.

PET is gaining increased interest by the development of new tracers. Although 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG)-PET has been validated to assess treatment efficacy of conventional cytostatic agents (79), the use of FDG-PET in detecting VEGFR TKIs responses is limited. An early metabolic response by FDG PET has been demonstrated for semaxanib (SU5416) within 2 weeks of therapy in a patient with metastatic RCC (80). Using oxygen-15 [^{15}O] labeled tracers such as ^{15}O-labeled water ([^{15}O]H_2O) and carbon monoxide ([^{15}O]CO_2), tissue perfusion and blood volume can be quantified (81). Also anti-cancer agents are increasingly being labeled with radioisotopes to serve as PET tracers. Sunitinib is the first VEGFR TKI that has been labeled with ^{18}F as PET tracer (82), however [^{18}F]sunitinib has not been evaluated in patients yet. In the future, radiolabeled VEGFR TKIs will most likely provide new information on their pharmacokinetic and pharmacodynamic action.

The data on functional imaging of the tumor response to VEGFR TKIs are limited, preliminary and not well validated. Rapid changes in vascular parameters are seen during treatment with VEGFR TKIs, which makes these parameters interesting markers for early prediction of tumor response and possibly progression-free and overall survival. Long term vascular consequences of therapy with VEGFR TKIs are largely unknown. Regarding tumor response evaluation, clinical benefit should be kept in mind. Our experience is that some patients have clinical benefit from VEGFR TKIs even while they have progressive disease. This may therefore be a reason to continue treatment.

5. TOXICITY

VEGFR TKIs have a distinct profile of side-effects. Toxicity observed with VEGFR TKIs has overlap with the toxicity associated with bevacizumab, indicating that these side effects are largely caused by inhibiting the same pathway. The differences in toxicity profiles between several VEGFR TKIs can be explained by differences in specificity and affinity. For some side-effects the etiology

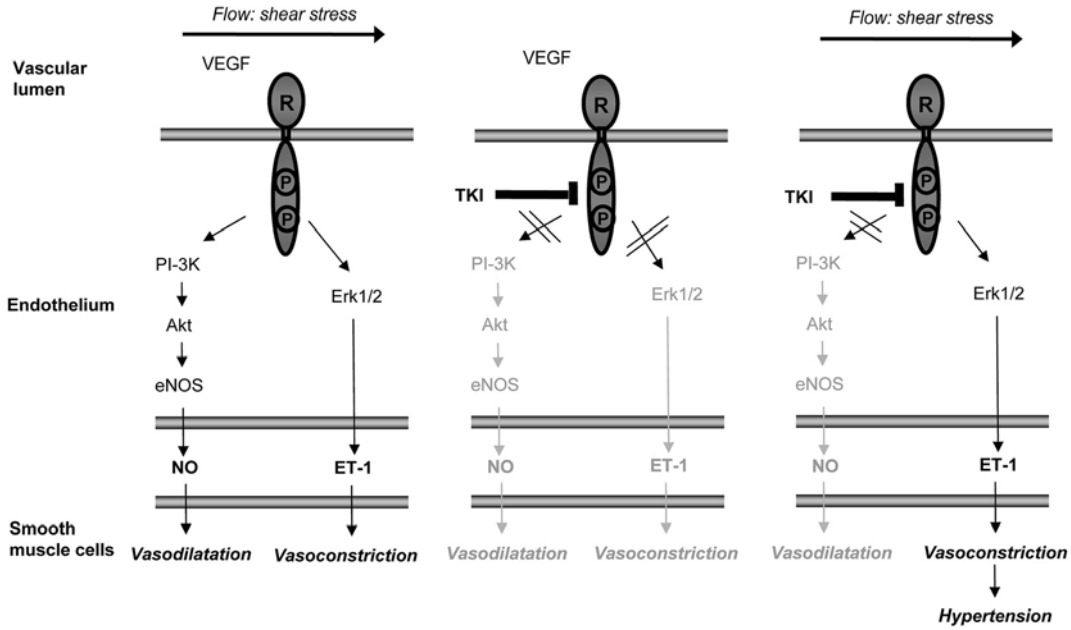

Figure 3. Role of vascular endothelial growth factor receptor (VEGFR)-2 in the vascular tone (a). Inhibition of VEGFR-2 by tyrosine kinase inhibitor (TKI) might result in a dysbalance between vasodilatation and vasoconstriction, leading to increased peripheral resistance and subsequent hypertension (b,c). R, receptor (extracellular domain), P, phosphorylation site (intracellular domain), PI-3K, phosphoinositide 3-kinase, eNOS, endothelium-derived nitric oxide synthase, NO, nitric oxide, ET-1, endothelin-1

remains poorly understood. Typical class specific side-effects will be discussed.

5.1. Hypertension

Administration of inhibitors of VEGF signaling often results in elevation of blood pressure with an incidence up to 50% in clinical trials (83-85). Grade 3 and 4 hypertension has especially been reported for VEGFR TKIs. This dose-dependent toxicity can occur within days and is reversible upon discontinuation of treatment. Insight into the mechanisms of VEGF-blood pressure effects is necessary for optimal clinical handling of this adverse event.

Bevacizumab treatment has resulted in a reduced density of microvessels and endothelial dysfunction, two mechanism that may be responsible for VEGFR TKI-induced hypertension (86). Evidence suggests that VEGFR-2 is involved in the regulation of the vascular tone (Figure 3a). It has been shown *in vivo* and *in vitro* that VEGFR-2 predominantly mediates the vasodilative and hypotensive effects of VEGF (87). So, it is conceivable that blocking VEGFR-2 causes vasoconstriction of the microcirculation. Activation of VEGFR-2 via phosphoinositide 3-kinase (PI3K) and its downstream serine protein kinase Akt induces endothelium-derived nitric oxide synthase (eNOS), resulting in the production of the potent vasodilator nitric oxide (NO) (Figure 3a) (88-92). Conversely, vasoconstriction is induced by endothelin-1 via protein kinase C and the Ras-Raf-ERK1/2 cascade (Figure 3a) (93). The VEGFR-2 TKI SU1498 blocks VEGF-induced activation of two intracellular pathways, namely endothelial Akt, eNOS and NO production, and ERK1/2 (Figure 3b) (94). SU1498, however, only blocks flow-induced activation of the Akt, eNOS and NO production, but not the activation of ERK1/2 (Figure 3c) (94). This suggests that the ERK1/2-endothelin-1 cascade dominates when VEGFR-2 is inhibited. It can be hypothesized that blocking VEGFR-2 by inhibitors of the TK domain will cause hypertension by inducing an imbalance between the PI3K-Akt-eNOS and ERK1/2 pathways (Figure 3c).

Tension control can be obtained with standard oral anti-hypertensive drugs, such as calcium-antagonists or beta-blockers (95). Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers are more rational to apply when proteinuria is also observed. Patients treated with VEGFR TKIs should have their blood pressure regularly measured, especially patients with pre-existent hypertension. Home blood pressure monitoring can be valuable to evaluate blood pressure during treatment with VEGFR TKIs (96).

Retrospective studies have identified grade 3 hypertension as a predictive factor for response to sunitinib (97, 98). This should be confirmed in large, prospective trials.

5.2. Proteinuria

Administration of bevacizumab is associated with an increased risk for proteinuria (99). Proteinuria is usually asymptomatic, rarely resulting in serious renal dysfunction. Less data on the incidence of proteinuria in VEGFR TKI trials are available. A preeclampsia-like syndrome characterized by hypertension and proteinuria has been described in seven patients treated with sunitinib

or sorafenib (100). In advanced thyroid cancer patients treated with axitinib, proteinuria was observed in 27% of the patients (41). Grade 3 proteinuria appeared to be a dose-limiting toxicity in a phase I study of KRN951 (101). Furthermore, in a phase I study of AMG706 grade 3 and 4 proteinuria was observed in 4% and 1% respectively (102).

The occurrence of proteinuria induced by anti-VEGF(R) therapy indicates the importance of VEGFR signaling in renal function (103). Podocytes express VEGF, which in turn activates glomerular endothelial cells. Inhibition of VEGF-dependent interactions between podocytes and glomerular endothelium by VEGFR TKIs might disrupt glomerular filtration leading to proteinuria. Increased blood pressure may contribute to the VEGFR TKI-induced proteinuria.

Patients treated with VEGFR TKIs should be monitored for proteinuria. In case of proteinuria grade 3 it is advised to reduce the dose or to discontinue treatment temporarily or permanently.

5.3. Cardiac toxicity

Cardiac toxicity has been observed during treatment with sunitinib and sorafenib (104). For sunitinib, two cases of congestive heart failure were reported in a phase I study (105) and an additional case on acute cardiac failure with a fatal outcome has been described (106). A phase III study with sunitinib in patients with metastatic renal cell cancer reported that 10% of patients had declines in left ventricular ejection fraction (LVEF) after a median treatment duration of 6 months (28). Additionally, two retrospective studies have investigated the sunitinib-induced cardiac toxicity (107, 108). Khakoo et al. reported that 6 of 224 (2.7%) patients treated with sunitinib developed heart failure which occurred soon after initiation of sunitinib and was not completely reversible in most patients, even after termination of sunitinib therapy (108). Chu et al. reported that 2 out of 75 patients with GIST had cardiac infarction and six developed congestive heart failure during sunitinib treatment (107). In these studies, hypertension and a decline in ejection fraction also occurred. Chu et al. have recently demonstrated that sunitinib exposure induced mitochondrial injury and cardiomyocyte apoptosis in mice and in cultured rat cardiomyocytes (107). Furthermore, during sorafenib treatment, increased cardiotoxicity has been observed in sunitinib-pretreated patients with metastatic renal cell cancer (109).

These results indicate that patients on VEGFR TKIs should be monitored carefully. Follow-up may consist of electrocardiogram and longitudinal measurements of LVEF. Special attention should be paid to patients with severe heart disease and coronary artery disease. With regard to cardiac toxicity, hypertension should be treated promptly.

5.4. Fatigue

Fatigue, asthenia and malaise are frequent symptoms observed in advanced cancer patients. Administration of VEGFR TKIs has been associated with the development of fatigue with an increased intensity. Mild to moderate fatigue has been reported in almost all phase I studies using VEGFR TKIs, and in some studies fatigue has been found to be dose-limiting. Establishing the cause of treatment-related fatigue is difficult. Anemia and renal or adrenal failure are not common events during VEGFR TKI treatment, and therefore not an obvious cause of the observed fatigue. Hypothyroidism, occurring during VEGFR TKI treatment, may be involved in some patients.

5.5. Hypothyroidism

The incidence of hypothyroidism in advanced cancer patients treated with sunitinib ranges from 2% to 80% (28, 110-113). The wide range can be explained by differences in defining hypothyroidism and the retrospective design of most of the studies. Other VEGFR TKIs are also capable of inducing hypothyroidism (114, 115).

Increased TSH concentrations are far more common than a change in T3/T4 levels during sunitinib therapy. A modest TSH increase with no related symptoms does not require supplemental therapy. In patients treated with VEGFR TKIs, T3/T4 monitoring is recommended. Profound TSH increases associated with low T3/T4 levels and overt hypothyroid symptoms should guide levothyroxine therapy. In some patients treated with sunitinib TSH increase was preceded by a short period of TSH decrease and T3/T4 increase, suggestive of thyroiditis (110) which may be associated with transient thyrotoxicosis (116).

Several mechanisms can be involved in VEGFR TKI-induced hypothyroidism. The thyroid gland is a hypervascularized tissue in which follicular cells have a close relationship with surrounding capillaries (117, 118). VEGFR TKIs might cause a significant regression of thyroidal capillaries, but also a disappearance of endothelial fenestrations (119), a decrease of vascular permeability (120), and capillary vasoconstriction (94). These effects may disturb delivery of iodide to the follicular cells, and/or result in regression of thyroid tissue, subsequently leading to reduced biosynthesis of thyroid hormones and an increased TSH response. TSH itself is known to increase the expression of VEGF and its receptors in the thyroid gland (118), which will induce proliferation of thyroid vessels and an increase in vascular permeability and vascular dilatation. This compensatory mechanism of TSH will increase the thyroid blood flow and facilitate iodide uptake. When the compensatory mechanism fails, overt hypothyroidism may develop.

Recently, two other underlying mechanisms of hypothyroidism have been proposed. In patients treated with sunitinib, hypothyroidism may be caused by impaired iodine uptake (121) as well as inhibition of thyroid hormone synthesis (112). With regard to the latter process, Wong et al. demonstrated *in vitro* that sunitinib inhibits peroxidase, the enzyme involved in the production of T4/T3 (112).

It is conceivable that VEGFR TKI induced hypothyroidism is multifactorial. Prospective studies to

further evaluate the incidence of VEGFR TKI-induced hypothyroidism and its relationship with fatigue and other possibly related symptoms like voice changes, cold intolerance and constipation, are needed.

5.6. Voice changes

Voice changes, hoarseness, or dysphonia have been reported in a number of clinical studies using VEGFR TKIs (115, 122-124). Disturbing the mucosal integrity by the use of VEGF(R) interfering agents might result in hoarseness. Incidental laryngoscopic examinations did not reveal any functional abnormalities of the vocal cords.

Voice changes may be a sign of hypothyroidism. However, voice changes occur already in the first week of treatment with VEGFR TKIs, while TSH increases usually occur after 8 weeks of treatment. Voice changes are reversible after discontinuation of VEGFR TKI treatment.

5.7. Gastrointestinal toxicity

Almost all clinical studies using VEGFR TKIs report mucositis of the upper and/or lower gastrointestinal tract leading to pain and diarrhea in a subset of patients. Stomatitis, usually described as a sore mouth without any overt blistering, is rather therapy-resistant, necessitating dose reduction or treatment interruption in severe cases. It is reversible after treatment discontinuation. Diarrhea has been reported in 43% of patients treated with sorafenib compared with 13% of patients treated with placebo (29). The diarrhea is usually manageable, but some patients need dose reduction or treatment discontinuation.

Mechanisms of the observed gastrointestinal toxicity remain unclear. It has been suggested that VEGF plays a role in physiological mucosal turnover and mucosal healing (125). It is also a possibility that TKIs affect other tyrosine kinases involved and this remains to be studied.

Bowel perforation is a less common but a serious side effect of anti-VEGF treatment. It occurred in 1.5% of colorectal cancer patients treated with bevacizumab (27) and in 11-15% of ovarian cancer patients treated with bevacizumab with or without erlotinib, an EGFR TKI (126, 127). Potential risk factors for this complication are previous irradiation, bowel metastasis, abdominal carcinomatosis, peptic ulcers, diverticulosis and recent surgery (128, 129). Local ischemia due to decreased perfusion may cause localized necrosis and subsequent perforation. When radiotherapy is combined with anti-angiogenic agents, the gastrointestinal tract is particular vulnerable (130, 131). In case of bowel perforation VEGFR interfering therapies should be withdrawn immediately. Although tumor cavitations and fistula formation upon VEGFR TKI treatment has been described (132), gastrointestinal perforations upon VEGFR TKI treatment have not been reported.

5.8. Cutaneous reactions

Hand-foot syndrome (HFS) is a painful palmar or plantar erythema associated with some cytostatic agents, such as doxorubicin, docetaxel and fluorouracil/capecitabine. In phase III trials using sorafenib or sunitinib, HFS has been observed in 30% and 20% of the patients, respectively (28, 29). HFS appears to be reversible after drug discontinuation. Bevacizumab is not related with cutaneous toxicity, suggesting that other TK receptors which are inhibited by sunitinib and sorafenib, like PDGFR and c-Kit, might be involved in the development of HFS. Since both VEGFR TKIs and some cytostatic agents can induce skin reactions of hands and feet, combining these agents might aggravate these reactions.

Other cutaneous side-effects like skin coloration (132, 133), subungual splinter hemorrhages (132, 134), and hair depigmentation (132, 135) have been described in patients treated with VEGFR TKIs. Yellow skin coloration can already appear after 1 week of sunitinib treatment and relates to yellow coloration of the urine. This might be due to the local deposition of the drug and its metabolites (132). Hair depigmentation has been observed in patients using sunitinib and pazopanib (GW786034) (132, 135), and might be due to the inhibitory effects on c-Kit (136).

5.9. Wound healing

Angiogenesis is thought to be critical for wound healing and blocking VEGF(R) signaling could interfere with this process (137, 138). An increased, but not significant, rate of wound healing complications has been observed in patients treated with bevacizumab (128, 139, 140).

In mouse models several VEGFR TKIs have been shown not to impair wound healing (141-143). This is a paradoxical finding which needs to be confirmed in clinical studies. Considering the short half life of VEGFR TKIs (i.e., 24 hours) compared with bevacizumab (i.e., 2-3 weeks), normally one week treatment interruption of VEGFR TKIs is recommended in the peri- or postoperative period.

5.10. Hemorrhage and thromboembolic events

Bevacizumab treatment has been associated with mostly non-serious bleeding events in patients with various tumor types. Serious, and even fatal, pulmonary hemorrhage was observed in lung cancer patients with central localization of squamous cell cancers (144, 145). Other infrequently occurring but serious bleeding events attributed to bevacizumab include gastrointestinal hemorrhages (146). VEGFR TKI studies also report bleeding events. In a phase III study comparing sorafenib with placebo in RCC patients, mild bleeding, like epistaxis, occurred more often in the sorafenib group (29). Studies with chemotherapy plus or minus vatalanib in patients with advanced colorectal cancer did not show an increase in bleeding events (45). Phase I trials using VEGFR TKIs, including vatalanib, have reported incidental bleeding events, which was fatal in some patients (101, 115, 147). Controlled trials are awaited to elucidate this association. Most of the bleedings do not occur in primary tumors or metastases, suggesting other vulnerable targets. Attention should be paid to patients with cerebral tumor lesions and patients on anticoagulant therapy.

Although thromboembolic events have not been reported for VEGFR TKIs administered as monotherapy,

when combined with chemotherapy, semaxanib, a VEGFR TKI no longer in clinical development, resulted in increased incidence of thromboembolic events (148). VEGF stimulates endothelial cells to produce tissue factor (149), an important regulator of the coagulation cascade, inducing thrombin and eventually clot formation. On the other hand, a low concentration of VEGF is needed to keep endothelial cells in a quiescent, anti-coagulant state. This may be explained by the fact that VEGF induces anti-apoptotic genes, and blockade of the VEGF pathway may lead to endothelial cell apoptosis, and consequently to a pro-coagulant state (150, 151). In addition, VEGFR inhibition reduces the proliferation rate of endothelial cells, and hence the capacity to cope with vascular damage. This may cause an increased exposure of the underlying ECM, which may lead to hemorrhage or thrombosis. This all supports that VEGF is also a maintenance factor for endothelial cells. Endothelial cells deprived of VEGF might be more vulnerable to prothrombic activity of cytostatic agents (152). Caution should therefore be taken when inhibitors of VEGF signaling are combined with chemotherapy (148, 153).

5.11. Hematological toxicity

A typical side-effect of classical cytotoxic agents is myelosuppression. Sunitinib and CHIR-258 can also cause neutropenia and this seems to correlate with inhibition of Flt3 (28, 154), since VEGFR TKIs lacking inhibitory activity against this target are not associated with neutropenia (102, 115, 122, 155). Sunitinib also induced moderate or severe thrombocytopenia in 40% of the patients compared to 4% in the placebo-treated patients. The Flt3-ligand is involved in early hematopoiesis, and primitive hematopoietic cells express its receptor (156). One should therefore be cautious in combining VEGFR TKIs, targeting Flt3, with classical cytotoxic agents. Increased serious neutropenia was observed with 50 mg sunitinib in combination with a FOLFOX-regimen compared to 37.5mg sunitinib (157).

Many advanced cancer patients have pre-existing disease- or therapy-related anemia before entering trials. In clinical trials comparing sunitinib or sorafenib with placebo, no increased anemia was observed in the experimental arm (29, 42). Preclinical experiments demonstrated that neutralizing VEGF signaling resulted in an increased production of erythropoietin (Epo) by the liver, leading to enhanced red blood cell counts (158). The impact of increased Epo levels during anti-angiogenic treatment is currently not known (159). Erythrocytosis and increased Epo levels have not yet been reported in the human setting.

5.12 Cerebral toxicity

Reversible posterior leukoencephalopathy syndrome (RPLS), has been associated with the use of VEGFR TKIs and bevacizumab, albeit at a low frequency (45, 160-164). RPLS is associated with headache, seizures, altered consciousness, and visual changes in association with characteristic posterior cerebral white matter edema on neuroimaging. Prompt recognition of the medical symptoms and discontinuation of the treatment is important in preventing permanent damage. The pathogenesis of RPLS remains unclear, but it appears to be related to disordered cerebral autoregulation and endothelial dysfunction (165).

In elderly patients on sunitinib treatment cognitive disorders have been described which disappeared promptly upon discontinuation of this drug (166). These elderly patients had pre-existent cerebral vascular abnormalities visualized as subcortical arteriosclerotic encephalopathy, which suggests that sunitinib may decrease the cerebral blood flow. Attention should therefore be paid to cognitive function in elderly patients on VEGFR TKIs.

6. PHARMACOLOGY AND DOSING

The intestinal absorption of most VEGFR TKIs is quick and peak plasma concentrations are observed within 1 to 7 hours. The plasma half-life (T1/2) differs among these agents (Table 1). For example, T1/2 of sunitinib is 41-86 hours and T1/2 of vatalanib is 3-6 hours (132, 167). This may indicate that the exposure to target receptors is more steady for the first agent and it might be a reason to give the second drug twice daily (167). The affinity of VEGFR TKIs to the three VEGF receptors is high (Table 1), but the clinical impact of differences in VEGFR-2 affinity between the various agents needs to be established. The affinity for other growth factor receptors, especially PDGFR, FGFR, c-Kit, Flt3, RET, differs substantially, which may significantly affect clinical activity and toxicity. Currently, data about the reversibility of binding to the receptors are lacking.

Compared to monoclonal antibodies, like bevacizumab, VEGFR TKIs are small molecules and penetration into any tissue, even brain tissue, is thought to be easy. However, the effects of VEGFR TKIs on brain tumors remain controversial (26, 168-171). Cediranib has proven to be effective in glioblastoma patients (26), sorafenib reduced the incidence of brain metastases in RCC patients (170) and response of brain metatases from RCC has been described for sunitinib (169, 171). On the other hand, a report on advanced RCC patients treated with sunitinib has suggested that brain metastases can be the first and/or only sign of tumor progression (168). An explanation may be that VEGFR TKIs are substrates for an upregulated P-glycoprotein mediated cellular efflux at the blood-brain barrier (172), resulting in a reduced penetration of these compounds.

VEGFR TKIs are predominantly metabolized in the liver by cytochrome P450 (CYP3A4). Therefore, the blood concentrations of the VEGFR TKIs can be influenced by co-medication with CYP3A4 modulators, which may affect the tumoral exposure to VEGFR TKIs (173). Since there is an interindividual variation in activity of CYP3A4, identification of factors that predict VEGFR TKI exposure are required to optimize treatment with VEGFR TKIs. The oral midazolam test measures the CYP3A4 activity and may be useful to predict whether

patients are predisposed to be overdosed or underdosed (174).

Since a large number of TKIs are substrates of CYP3A4, combining VEGFR TKIs with other TKIs increases the chance of drug-drug interactions. Significant pharmacokinetic interactions between VEGFR TKIs and TKIs targeting other receptors have been described (50, 175), although not in all studies (49, 51). Many combination regimens of VEGFR TKIs and cytostatic agents are currently under investigation. Pharmacokinetic analyses, performed so far, do not show significant drug-drug interaction with cytostatic agents. Pharmacokinetic evaluation in combination regimens is important to reassure sufficient plasma levels without the risk of accumulation or increased toxicities.

Most VEGFR TKIs are administered daily in a continuous dosing schedule, since it is widely believed that continuous inhibition of the VEGF receptors is needed for an optimal effect. Sunitinib is administered in an intermittent schedule of 4 weeks followed by a 2-week rest period meant to recover from toxicities. However, in the 2-week rest period some patients, especially those with an initial tumor response, experience a rapid clinical deterioration (within days), which may necessitate continuous administration of sunitinib. The rapid rebound during the rest period is intriguing and may be due to early regrowth of the tumor vasculature (176), or, more likely, to tumoral edema (177). In several studies VEGF levels increase during VEGFR TKI therapy (26, 178). This may have consequences when the VEGFR TKI is temporarily discontinued. Increased vascular permeability leading to tumoral edema will be the first symptom.

7. CONCLUSIONS

VEGFR TKIs are increasingly being integrated in treatment regimens for cancer patients and efficacy data of these regimens are promising. Understanding the role of various ligand-receptor pathways in tumor biology in general and in a specific tumor type in a specific patient will guide future applications. Regimens combining VEGFR TKIs with other anti-cancer strategies must be evaluated and optimized for each agent and in each setting. This is even true for any co-medication which modulates CYP3A4. In settings where chemo- and/or radiotherapy is considered the standard of care, anti-angiogenic agents must be introduced carefully to minimize toxicity. Although VEGFR TKIs are generally well tolerated and are associated with manageable side-effects, they have distinct toxicity profiles which are partly due to their activity towards other, may be unknown, TK receptors. It is important to realize that their long-term effects on normal human cell and tissue physiology are largely not known. Considering the promising efficacy in adjuvant settings, VEGFR TKIs will be administered to cancer patients for longer periods. At present it is not clear which long-term and secondary consequences can be expected from VEGFR TKI-induced side-effects such as hypertension. Moreover, long-term effects of VEGFR TKIs on tumor biology remain to be investigated, since VEGFR TKIs generally does not result in complete tumor remission. Focus should also be given to long term consequences of inducing tumor hypoxia. Hypoxia may induce a rebound complex angiogenic response which also may affect tumor metastasis. A better understanding of these effects can help to reduce acquired resistance and to design better combination regimens that finally will improve patient outcome.

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