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The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; A review

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ABSTRACT

Clinical experience with vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors is rapidly increasing, and some compounds have already been approved for regular anticancer treatment.

Apart from their activity, much attention has been focussed on the clinical toxicity profile of these compounds.

This review describes the most frequently occurring side-effects of both antibodies and tyrosine kinase inhibitors and discusses some of the underlying mechanisms. Some practical guidelines for treatment of the side-effects are given.

1. Introduction

Angiogenesis, the formation of new blood vessels sprouting from the pre-existing vasculature, is critical for the development and subsequent growth of human tumors and is a prerequisite for the formation of metastases. Various proangiogenic factors secreted by tumor cells and / or host factors stimulate endothelial cells to proliferate and to form new, qualitatively poor and often leaky new blood vessels. As few as 60–200 tumor cells can initiate the process of angiogenesis. Although various proangiogenic factors such as basic fibroblast growth factor (bFGF) and platelet derived growth factor (PDGF) are involved, the Vascular Endothelial Growth Factor (VEGF) family, and especially isoform VEGF-165, is the predominant proangiogenic factor. VEGF exerts its activity through binding to several high-affinity transmembrane endothelial cell receptors, most notably VEGF receptors (VEGFR) types 1 and 2 (VEGFR-1 or Flt-1 and VEGFR-2 or KDR/Flk-1). Binding of VEGF to these receptors leads to intracellular receptor phosphorylation which initiates various intracellular downstream receptor pathways leading to endothelial cell proliferation and blood vessel formation. (Fig. 1) VEGF binding to VEGFR-3 expressed on the lymphatic endothelium initiates lymphangiogenesis.

Angiogenesis is a pivotal target for the development of a totally new class of inhibitory agents. With regard to mechanisms to inhibit VEGF induced angiogenesis, both VEGF and VEGFR neutralizing antibodies and small molecule VEGFR tyrosine kinase inhibitors have been developed. VEGF targeted antibodies bind to the ligand VEGF prior to its connection to the natural endothelial receptor, while VEGFR targeted antibodies bind to the endothelial receptor before the natural ligand VEGF can

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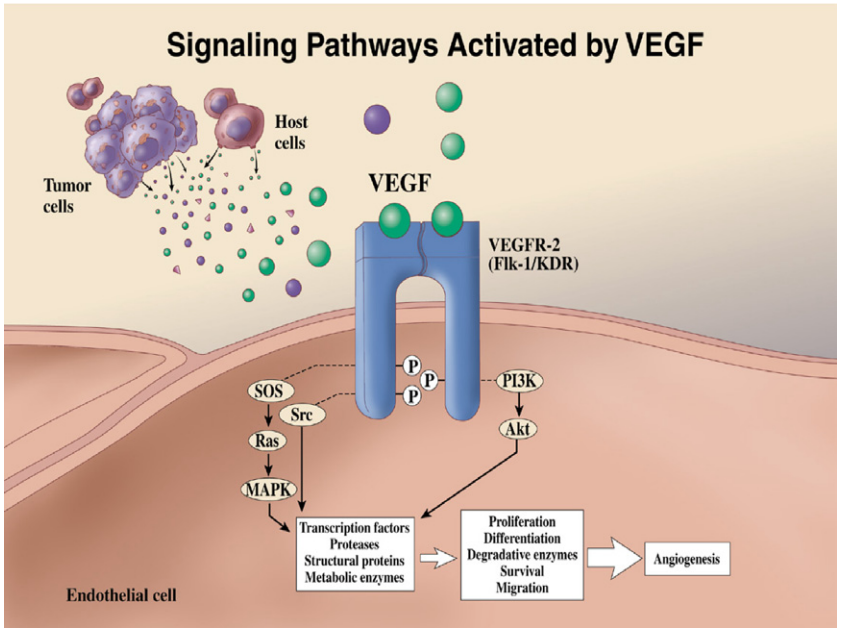

Fig. 1 – Signaling pathways activated by VEGF.

do so. In both circumstances normal ligand-receptor interaction is blocked, and receptor phosphorylation and downstream pathway activation are inhibited.

Small molecule VEGFR tyrosine kinase inhibitors act at the intracellular domain of the endothelial receptor where they inhibit the initial phosphorylation steps that follow ligand-receptor interaction.

Since VEGF plays a role in such physiologic processes as wound healing and the female reproductive cycle, and seemingly also has a role to play in many other tissues and in conditions like mucosal integrity, inhibiting the actions of this protein theoretically might have various different (side-) effects.

The VEGF targeting antibody bevacizumab was the first angiogenesis inhibitor to be approved, in combination with chemotherapy, for regular prescription in the USA, Europe and elsewhere, and the VEGFR tyrosine kinase inhibitors sorafenib and sunitinib have recently followed, indicating that angiogenesis inhibition is becoming an established and available anticancer treatment option in daily practice. These achievements have greatly boosted enthusiasm for further development and testing of a large group of new angiogenesis inhibitors, and currently new VEGF and VEGFR targeting antibodies as well as a large number of VEGFR tyrosine kinase inhibitors are undergoing clinical testing, with new activity and toxicity data from these studies becoming available on an almost continuous basis.

With regard to toxicity, angiogenesis inhibitors in general lack the typical and often cumbersome side-effects of cytotoxic anticancer agents, but it cannot be concluded that these agents are completely devoid of toxicity. The recognition of certain toxicity patterns and the possibilities how to treat them is therefore becoming increasingly important as more and more compounds will probably come to the market.

This review provides an overview of the most frequently occurring side-effects of the VEGF(R) targeting angiogenesis inhibitors that have been reported to date. As some typical class specific side-effects have emerged, we will discuss these effects in more detail and we will speculate on potential pathophysiological mechanisms and rational treatment options. For clarity, we will describe and discuss the data from antibodies and small molecule tyrosine kinase inhibitors as two separate groups.

2. VEGF(R) neutralizing antibodies

Bevacizumab is a humanized recombinant monoclonal antibody binding to VEGF prior to its attachment to the natural endothelial receptors VEGFR-1 and VEGFR-2. In the first phase I single-agent study performed, exploring a number of pre-defined dose levels, side-effects attributable to bevacizumab were asthenia, headache, and nausea. Although one case of grade 3–4 intracranial bleeding was noted, a causal relationship with bevacizumab was not considered. With regard to hypertension, “minor changes in blood pressure were noted to be associated with rhuMAb VEGF administration”. Two bleeding episodes were considered to be disease related, and none of the observed side-effects was considered to be dose limiting.[1]

Current extensive clinical experience with the agent, given as single agent or, most often, in combination with various cytotoxic chemotherapy regimens for a wide range of indications, has revealed a recognizable pattern of drug related side-effects, of which hypertension, asymptomatic proteinuria, thromboembolic as well as bleeding complications, and gastrointestinal perforations are most prominent.

Drug-related hypertension of any degree occurs in up to 30% of patients, but has usually been found to be easily manageable.[2–6]

Asymptomatic proteinuria of any degree occurs in up to 40% of patients and will only be detected with strict follow-up. Drug-induced nephrotic syndrome has been described

sporadically.[6] The potential causal relationship between bevacizumab induced hypertension and proteinuria is not fully clear, as both side-effects can occur independent from each other. Proteinuria, however, is a well known consequence of hypertension induced microvascular damage of the glomerulus, and therefore a potential causal relationship between these two phenomena is very well conceivable.

Arterial thromboembolic complications, usually presenting as stroke, transient ischemic attack, myocardial infarction or angina pectoris occur with increased frequency in patients treated with bevacizumab, most notably in patients aged >65 years and in those with a previous history of such an event.

Non-serious bleeding complications such as epistaxis and cutaneous bleedings have also been observed to occur more frequently in patients with various tumor types treated with bevacizumab, and a number of lethal cases of haemoptysis have been described in patients with centrally located squamous cell non-small cell lung cancer.[6]

In randomized trials in colorectal cancer, gastrointestinal perforations occurred more frequently in patients treated with bevacizumab than in those patients who only received chemotherapy.[2,7] Recently gastrointestinal perforations were also reported in patients with advanced ovarian cancer being treated with bevacizumab, leading to the premature closing of one trial due an unexpected 11% frequency of this potentially life threatening complication.[8–10]

Other antibodies (HuMV833, VEGF-trap or AVE0005 and IMC-1121B) are in early clinical development, and their stage of development currently precludes the possibility on firm conclusions of their side-effect profile.[11–14] HuMV833 is a recombinant humanized IgG4k monoclonal antibody targeting VEGF, VEGF-trap or AVE 0005 is comprised of the extracellular domains of VEGFR-1 and VEGFR-2 fused to human IgG1 Fc and binds to VEGF prior to its binding to the natural receptor, and IMC-1121B is a human IgG antibody targeting VEGFR-2.

3. VEGFR tyrosine kinase inhibitors

When compared to antibodies targeting VEGF or VEGFR, the modern VEGFR tyrosine kinase inhibitors share the advantage of oral availability, which nowadays is considered to be a major convenience benefit for patients. Currently, a large number of these compounds are undergoing clinical studies, ranging from phase I to large randomized phase III studies.

The actual stage of clinical development of each compound, the individual target inhibitory profile, most frequently used schedules of administration and an overview of the most prominent and / or frequently occurring side-effects are summarized in Tables 1–4.

SU 5416 was the first VEGFR tyrosine kinase inhibitor to be tested clinically. This compound was administered intravenously and had to be dissolved in cremophor, yielding anaphylactic reactions in a number of patients. Eventhough the clinical development of this compound has already been stopped, we present toxicity data from this compound as a kind of historical background. We will further focus on orally available compounds that are currently being developed and tested in clinical studies.

As can be seen in Table 4, a spectrum of different side-effects has been observed, a number of which can be considered to be intrinsically related to the inhibitory effects of VEGF activity. In addition, a clear overlap between the side-effects from small molecule tyrosine kinase inhibitors and monoclonal antibodies targeting VEGF is observed. For the small molecules inhibiting a range of tyrosine kinases apart from VEGFR-tyrosine kinase, it is sometimes difficult to which specific inhibition one should attribute a side-effect. This has to be taken into consideration when reading the following. Apart from this, most data that have been collected for this review come from abstracts that have been published, with only a relatively small number of full papers being published.

Table 1 – Angiogenesis inhibitors in clinical studies; VEGF(R) neutralizing antibodies and VEGFR tyrosine kinase inhibitors

Compound	Company	Phase of clinical development
Monoclonal antibodies		
Bevacizumab	Roche	Registered
VEGF Trap	Sanofi-Aventis / Regeneron	Phase 2/3
HuMV833	Protein Design Laboratories	Phase 1
IMC-1121B	Imclone	Phase 1
VEGFR-TKI		
AEE 788	Novartis	Phase 2
AG 013736 (axitinib)	Pfizer	Phase 2
AMG-706	Amgen	Phase 2
AZD 2171	Astra Zeneca	Phase 2
AZD 6474	Astra Zeneca	Phase 2
BAY 43–9006 (sorafenib)	Bayer	Registered
BAY 57–9352 (telatinib)	Bayer	Phase 1
BIBF 1120	Boehringer Ingelheim	Phase 1
BMS 582664	Bristol Meyers Squibb	Phase 1
CHIR 258	Chiron	Phase 1
CP-547,632	Pfizer	Phase 2
GW 786034 (pazopanib)	GlaxoSmithKline	Phase 2
KRN 951	Kirin	Phase 1
PTK 787 (vatalanib)	Novartis/Schering	Phase 3
SU 5416 (semaxanib)	Pfizer	Phase 3*
SU 6668	Pfizer	Phase 2*
SU 11248 (sunitinib)	Pfizer	Registered
SU 14813	Pfizer	Phase 2
XL 647	Exelis	Phase 1
XL 999	Exelis	Phase 2
ZK 304709	Schering	Phase 1

4. Side-effects

When angiogenesis inhibitors were to enter clinical studies, the hope and expectation, based upon findings in preclinical studies, was that this class of anticancer agents would be essentially non toxic and maybe even completely devoid of toxicity. Indeed, and as mentioned earlier, many of the

Table 2 – Reported target inhibition of angiogenesis inhibitors in clinical studies

Compound	VEGFR1/2	VEGFR 3 FLT-4	PDGFR	FGFR	C-Kit	EGFR 1	HER2
Monoclonal antibodies							
Bevacizumab	VEGF						
VEGF Trap	VEGF						
HuMV833	VEGF						
IMC-1121B	X						
VEGFR-TKI							
AEE 788	X	X	X		X	X	X
AG 013736	X	X	X		X		
AMG-706[a]	X	X	X		X		
AZD 2171	X	X	X		X		
AZD 6474[a]	X					X	
BAY 43–9006[a,b]	X	X	X				
BAY 57–9352	X		X				
BIBF 1120	X		X	X			
BMS 582664	X	X		X			
CHIR 258	X		X	X	X		
CP-547,632	X						
GW 786034	X		X		X		
KRN 951	X		X		X		
PTK 787	X	X	X		X		
SU 5416	X				X		
SU 6668	X		X	X	X		
SU 11248[a]	X		X		X		
SU 14813	X	X	X		X		
XL 647	X					X	X
XL 999[c]	X	X	X	X			
ZK 304709[d]	X		X				

a Also inhibits RET.
b Was initially considered to be a selective Raf kinase inhibitor.
c Also inhibits SRC kinase.
d Also inhibits Cycline Dependent Kinases 1,2,4,7,9.

cumbersome and potentially life-threatening side-effects of commonly used cytotoxic anticancer agents such as alopecia, profound myelosuppression, incapacitating peripheral sensory neuropathy, renal toxicity and severe gastrointestinal toxicity have not or only sporadically been described. With ongoing development of more potent angiogenesis inhibitors (based upon IC_{50} values observed in *in vitro* studies), and with ongoing clinical experience of the earlier developed compounds, it has become clear that side-effects nonetheless do occur, and that a recognizable pattern of drug related side-effects exists. Here we describe the most prominent of these side-effects, will speculate on pathophysiological mechanisms, usually based on local VEGF inhibition, and will discuss the rationale and efficacy of some treatment options.

4.1. *Hypertension and cardiovascular events*

Hypertension is the most prominent side-effect of almost all angiogenesis inhibitors, both monoclonal antibodies and VEGFR tyrosine kinase inhibitors. This phenomenon underscores the important physiological role of VEGF in regulating vasomotor tonus and maintaining blood pressure.

It has been demonstrated in animal models that VEGF induces endothelium-dependent coronary artery relaxation. In animals and man, VEGF preferentially dilates small arterioles and venules, and by doing so it induces a decrease in blood pressure. VEGF induces the phosphorylation of endothelial nitric oxide synthase (eNOS) resulting in an increased production of endothelial type nitric oxide (NO), which directly acts on endothelium. This effect of VEGF on endothelial cells is responsible for angiogenesis. Of interest to mention here is the correlation that has been found between decreased VEGF production and an increased prevalence of hypertension with increasing age. Considering this vasodilative effect of VEGF, it can be understood that functional blockade will induce vasoconstriction and hypertension.

Rarefaction, the reduced density of microvessels in tissues and organs is another mechanism that can lead to hypertension. Rarefaction could be the result of decreased angiogenic activity of VEGF, and therefore might be the connecting link between VEGF inhibition and hypertension. However, while rarefaction has been considered to play a role in the development of hypertension, it is not fully clear whether it should be considered primarily as cause or consequence of hypertension.[15] In clinical studies with angiogenesis inhibitors, drug-induced hypertension almost invariably is reversible upon discontinuation of treatment, and this observation could argue against a mere structural or anatomical explanation such as rarefaction for drug-induced hypertension. In addition, it has been reported for some of the more recently developed potent VEGFR tyrosine kinase inhibitors that hypertension can occur within hours following the first drug administra-

Table 3 – Most frequently used schedules of administration in clinical studies

Compound	Administration schedule
Monoclonal antibodies	
Bevacizumab	IV days 0, 28, 35, and 42 / every 14 days
VEGF Trap	SC once weekly or IV once every 14 days
HuMV833	IV days 1, 15, 22 and 29
IMC-1121B	IV once weekly
VEGFR-TKI	
AEE 788	Continuous OD
AG 013736	Continuous OD or BID
AMG-706	21 days OD, 7 days off / continuous OD
AZD 2171	Continuous OD
AZD 6474	Continuous OD
BAY 43–9006	7/21/28 days OD, 7 days off / continuous OD
BAY 57–9352	Ongoing study
BIBF 1120	28 days OD, 7 days off / continuous OD and BID
BMS 582664	Continuous OD
CHIR 258	7 days on, 7 days off / continuous
CP-547,632	
GW 786034	3 times weekly to to continuous OD
KRN 951	Ongoing study
PTK 787	Continuous BID
SU 5416	IV twice weekly
SU 6668	Continuous BID, TID
SU 11248	28 days OD, 14 days off
SU 14813	28 days OD, 7 days off / Continuous
XL 647	Intermittend schedule
XL 999	IV 4-hour infusion q 14 days
ZK 304709	Ongoing study

Compounds are administered orally unless mentioned otherwise
IV intravenously
SC subcutaneously.

tion. This also argues against structural or anatomical changes in the vasculature. Whether acute vasoconstriction or the release of so far unrecognized vascular active factors could be responsible for this (sub) acute rise in blood pressure still remains to be determined.

Taking into consideration the important role of VEGF as a vasodilative glycoprotein, one could hypothesize that if an angiogenesis inhibitor targeting VEGFR does not induce a certain degree of hypertension, sufficient plasma levels and/or biological activity has been achieved. From a pharmacodynamic point of view therefore, hypertension could be considered as a new pharmacodynamic endpoint for phase I studies with these agents. This recommendation is in accordance with some previously published results.[16]

In studies with bevacizumab, hypertension of any degree occurs in up to 30% of cases but is considered to be easily manageable with conventional antihypertensive drugs such as calcium channel blockers, angiotensin II antagonists or angiotensin converting enzyme inhibitors in the vast majority of cases. Drug-induced hypertension has only sporadically been dose limiting, which in the Common Technology Criteria for Adverse Events (CTCAE) version 3.0 would mean grade 4, i.e. "life threatening consequences (e.g.hypertensive crisis)", and has resulted in permanent drug discontinuation in only a very small number of patients. In studies with VEGF trap and almost all VEGFR tyrosine kinase inhibitors, hypertension has also been observed, with a number of these events being dose limiting, necessitating short-lasting drug discontinuations.[17–20] In a number of cases dose reduction had to be pursued following the inability to adequately control hypertension by two antihypertensive drugs at their respective optimal dose.

In otherwise healthy patients in whom drug induced hypertension occurs, it usually has been found to be easily manageable with antihypertensive drugs. Currently, in a number of early clinical studies with some of the new angiogenesis inhibitors, patients with established hypertension or patients treated with antihypertensive drugs are being excluded from participation. However, as hypertension is a very frequently occurring phenomenon in the aging population, which happens to be the population in which cancer is also most frequently occurring, we advocate that patients with a pharmacologically well controlled hypertension (indicating a blood pressure of up to 140/90 mm Hg) should be given the opportunity to be enrolled in any of these studies. Under these circumstances it is obvious that meticulous follow-up of the blood pressure is mandatory and treatment of drug induced hypertension is intensified immediately when indicated. Instructing patients to measure their blood pressure at home and contact their physician when it exceeds a predefined level, which should be based on the blood pressure at enrollment, could make an almost continuous control and adequate intervention well possible. If in such a "population study" an angiogenesis inhibitor would turn out to be unsafe and maybe even detrimental for patients, it is very unlikely that such a drug will ever get approval for regular use.

With regard to drug induced hypertension, the vasoconstrictive activity of the VEGFR inhibiting angiogenesis inhibitors seems to favour antihypertensive treatment with vasodilative drugs such as angiotensin converting enzyme inhibitors, angiotensin II blockers or calcium antagonists. In fact, in many of the studies that specifically describe their antihypertensive strategy, treatment with any of these drugs indeed resulted in adequate control of hypertension in most patients. In addition, some recently presented preclinical data seem to support such a strategy as well.[21] Based upon the mechanism of action of angiogenesis inhibitors, antihypertensive treatment with diuretics or beta blockers would probably result in less adequate control, although data with regard to effectiveness of various classes of antihypertensive agents are lacking. Finally it is obvious that in protocols of clinical studies with angiogenesis inhibitors, clear guidelines and recommendations for antihypertensive treatment must to be included.

If any drug induced hypertension cannot be controlled by two antihypertensive drugs that are given at their maximal dose, or when hypertension is accompanied by signs or symptoms of end organ damage such as hypertensive retinopathy, kidney function abnormalities like progressive proteinuria, or any sign or symptom of cardiovascular morbidity, treatment with angiogenesis inhibitors should be interrupted or the dose should be decreased.

Due to the common pathophysiological mechanisms of microvascular and macrovascular damage, it is conceivable

Table 4 – Most frequently occurring drug related side-effects described in clinical trials

	RR ↑	Prot	TE	Bleed	Perf	Voice	Muc	Fatigue	Liver	Diarr	Skin	N/V	Abd	HFS	Head	CNS	Myel	Ref
MOAB																		
Bevacizumab	+	+	+	h	+	-	-	+	-	-	-	-	-	-	-	-	-	1–10
HuMV833	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	11
VEGF-trap	+	+	-	-	-	+	-	-	+	-	-	-	-	-	-	-	n	12,13
IMC-1121B	-	+	+	-	-	-	-	+	+	-	-	+	-	-	-	-	-	14
VEGFR-TKI																		
AEE 788	+	+	-	-	-	-	+	+	+	+	+	+	-	-	-	-	t,n	56,57
AG-013736	+	+	+	h,gi	-	+	+	+	+	+	-	+	-	-	-	s,d	t	58
AMG 706	+	-	+	-	-	-	-	+	-	+	+	-	-	-	+	d	-	59,60
AZD 2171	+	+	+	he,ic	-	-	+	+	+	+	-	+	+	-	-	d	-	21,27,61–63
AZD 6474	+	+	-	h	-	-	+	+	+	+	+	-	-	-	-	-	t	19,64–67
BAY 439006	+	-	+	h	-	-	+	+	+	+	-	-	+	+	-	-	n	68–79
BAY 57-9352	+	+	-	-	-	+	-	-	-	+	+	+	-	+	+	-	-	80–81
BIBF 1120	-	-	-	-	-	-	-	+	+	+	-	+	+	-	-	-	-	82–84
BMS 582664	+	-	-	-	-	-	-	+	+	-	-	-	-	-	-	d	-	85
CHIR 258	+	-	-	-	-	-	-	+	-	+	-	+	-	-	+	-	-	86
CP 547633	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	87,88
GW 786034	+	-	-	gi	-	-	-	+	+	+	+	+	+	-	-	-	-	89,90
KRN 951	+	+	-	ic	-	+	+	+	-	+	+	+	+	-	+	a	-	17
PTK 787	+	-	+	h	-	-	-	+	+	+	+	+	+	-	+	d,a	-	20,49,50,91,92
SU 5416	-	-	+	-	-	+	-	+	+	+	-	+	-	-	+	d	a	93–97
SU 6668	-	-	-	-	-	-	-	+	-	-	-	+	+	+	-	-	t	98–104
SU 11248	+	-	-	ic	-	+	+	+	+	+	+	+		+	-		t	105–107
SU 14813	+	-	-	-	-	-	+	+	-	-	-	-	-	-	-		t,n	108
XL 647	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	109
XL 999	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	d	-	110

MOAB: monoclonal antibody
VEGFR-TKI : vascular endothelial growth factor receptor tyrosine kinase inhibitor
RR↑: hypertension
Prot: proteinuria
TE: thromboembolisms
Bleed: (h) haemopthysis, (gi) gastrointestinal bleeding, (ic) intracranial bleeding, (he) hematuria
Perf: visceral perforations
Voice: changes in voice, i.e. hoarseness
Muc: mucositis
Diarr : diarrhea
Liver: transaminase elevations
N/V: nausea and/or vomiting
HFS: hand foot syndrome
Head: headache
CNS: other cerebral toxicities: (s) seizures, (d) dizziness, (a) ataxia
Myel: myelosuppresion (a) anemia, (n) neutropenia and/or (t) thrombocytopenia
Ref: references.

that drug induced hypertension could be accompanied by proteinuria, cardiovascular events and bleeding complications.

Indeed, all these events have been observed in studies with many of the VEGFR targeting angiogenesis inhibitors, albeit that a direct or causal relationship between any of these events and an increased blood pressure is not always obvious. With regard to the pathophysiological mechanism of drug induced proteinuria, a striking resemblance with preeclampsia and pregnancy induced hypertension (PIH) exists. Under these circumstances lower levels of circulating VEGF have been found when compared to normal pregnancies. For the proteinuria that is universal under these circumstances, damaged or dysfunctional glomerular endothelium as a hallmark of microvascular disease and leading to protein loss is considered to be the underlying feature.[22] Drug induced proteinuria due to the use of angiogenesis inhibitors has only very rarely resulted in an overt nephrotic syndrome or the need for dialysis, but this usually non-symptomatic finding can still have a great potential impact on a patient's well-being. Therefore, strict follow up of proteinuria in all patients treated with angiogenesis inhibitors seems mandatory. This can be easily accomplished with the use of a standard dipstick method, with 24-hour urinalysis for optimal quantification being performed in case of progressive proteinuria. In case of overt or progressive proteinuria, the dose of angiogenesis inhibitors has to be lowered, or treatment should be interrupted or even permanently stopped. These measures should be taken without exception, even considering the fact that many of the typical cancer patients treated in a palliative setting most likely will never develop the ultimate consequences of proteinuria.

Cardiovascular and cerebrovascular thromboembolisms are some of the most devastating results of macrovascular damage that in turn should be considered to be the final result of preexisting and progressive microvascular disease. Clinically and epidemiologically these events are often found to be associated with long-standing hypertension and microvascular damage, but on the other hand it is well known that patients suffering from metastatic malignant disease without cardiovascular risk-factors are at increased risk for these complications. Studies performed in patients with metastatic disease therefore are likely to report an excess of these events, but apart from these considerations, there is an apparent high incidence of transient ischemic attacks or stroke, angina pectoris and myocardial infarctions in patients being treated with angiogenesis inhibitors. Risk factors for any of these events are increased age, most notably those patients over 65 years, and a previous history of such an event. With regard to the underlying mechanism of action, dysfunctional or damaged endothelium is considered, whereas platelets as carriers of VEGF have also been suggested to play a role in the increased incidence of these acute and sometimes life-threatening events.[23] With regard to safety, it is not clear whether patients with any kind of 'minor' thromboembolic event in their medical history can be treated safely with angiogenesis inhibitors, and whether prophylactic or full dose therapeutic anticoagulant therapy can be given safely in combination with angiogenesis inhibitors as an increased risk of bleeding could be anticipated under these circumstances. Although there are data suggesting that bevacizumab and anticoagulation can be combined safely, it is obvious that patients suffering from any major thromboembolic event considered to be attributable to an angiogenesis inhibitor should stop their treatment immediately pending additional diagnostic and therapeutic decisions.[24] Although data with respect to incidence and management of cardiovascular and cerebrovascular events from bevacizumab are more mature than those from the various VEGFR tyrosine kinase inhibitors, it is conceivable that, considering the fact that the VEGF inhibitory effects of the various classes of angiogenesis inhibitors are comparable, the inherent risks for any such event is theoretically comparable. As a matter of fact, various different vascular events have been described following exposure to VEGFR tyrosine kinase inhibitors. It is thus also conceivable that the apparent differences in incidence of any cardiovascular thromboembolic event observed between bevacizumab and small molecules therefore may be related to the yet relatively small number of patients that have been exposed to some of the small molecules.

4.2. *Bleeding*

VEGF is an important proangiogenic stimulus under such physiological processes as endometrial recovery following menstrual bleeding, wound healing and surgical adhesion formation. Under these circumstances, tissue damage is a strong stimulus for local hypoxia inducible transcription factor-alfa (HIF-1α) production, which induces VEGF expression that subsequently leads to the formation of new blood vessels and wound healing. VEGF thus plays a central role in tissue integrity and wound repair, and VEGF inhibition may thus lead to decreased tissue integrity (like in mucositis), disturbed wound healing and bleeding complications of various kinds.

An increased rate of wound healing complications in patients on treatment with bevacizumab has indeed been observed, and currently a period of at least 28 days is recommended between the last administration of bevacizumab and any elective surgical procedure.[25]

Treatment with bevacizumab has resulted in an increased bleeding tendency in patients with various tumortypes, with most bleedings, however, being relatively limited and non-serious. Epistaxis and subcutaneous bleedings are examples of such uncomplicated bleedings that usually can be treated conservatively. In studies in non-small cell lung cancer, however, pulmonary bleedings were observed in a number of patients, some cases of which were fatal.[6] All these fatal events occurred in patients with centrally located squamous cell lung cancer, and it is hypothesized that presence or the development of tumor cavitation, probably as a sign of antitumor activity of chemotherapy and bevacizumab, underlies these events. Patients with centrally located squamous cell lung cancer are therefore currently excluded from bevacizumab treatment. It is obvious that in other types of (lung) cancer bevacizumab should also be stopped immediately in case of major tumor related bleeding.

Although the exact mechanism underlying the bleeding tendency following VEGF inhibition remains somewhat speculative, one can imagine that the combination of local hypoxia and qualitatively inferior blood vessels in the vicinity of primary tumors or metastases renders these processes

extremely susceptible to bleeding following VEGF inhibition. However, the number of clinical relevant bleedings originating in primary tumors or metastases so far has only been small, and, taken as an example of clinical relevant bleedings, most intracranial bleedings that were observed in patients treated with angiogenesis inhibitors occurred in patients without cerebral metastases.

Whether VEGF activity is inhibited through monoclonal antibodies or tyrosine kinase inhibitors does not seem to be essential, and in fact, apart from the previously described bleeding events related to bevacizumab, various tyrosine kinase inhibitors of VEGF have also been found to be associated with bleeding manifestations, some of which have been fatal as well.[17,26,27] Whether these events were related to hypertension or other signs or symptoms of cardiovascular morbidity is largely unknown, and whether the presence of cerebral metastases increases the risk of such an event is also nut fully clear. However, in order to prevent as much as possible these devastating complications, the current accepted strategy to exclude patients with known cerebral metastases and those on full dose anticoagulant therapy from treatment with any angiogenesis inhibitor seems rational and prudent.

The management of any drug induced bleeding complication does not differ from normal treatment options, but of course the interruption of treatment with the potential causative agent is crucial.

4.3. *Perforations*

Treatment with some VEGF inhibiting angiogenesis inhibitors is associated with an increased rate of gastrointestinal perforations, either gastric, small bowel, or colonic perforations. Clinically, a number of potential risk factors has been identified, amongst which are aspirin or NSAID use, chronic colonic inflammatory disease, gastric ulcer disease, recent surgery, abdominal radiation and obstruction due to local tumor growth. In a number of these situations high mucosal levels of VEGF are found, rendering tissues potentially vulnerable to VEGF blockade. Local ischemia due to decreased local perfusion could also lead to localized necrosis and perforation.[28] Apart from patients with colorectal cancer, patients with advanced ovarian cancer have been found to be susceptible to gastrointestinal perforations.[8–10] In these patients, a comparable accumulation of risk factors could be assumed. While until recently gastrointestinal perforations had only been described following exposure to bevacizumab, two cases of gastrointestinal perforations, one of which was lethal, were recently reported in patients treated with a VEGFR tyrosine kinase inhibitor. It remains to be investigated whether VEGF inhibition as such is the underlying mechanism for these events, and not so much the drug that induces it, or whether there is a different incidence of this side-effect between monoclonal antibodies and small molecules.

Gastrointestinal perforations will most likely present as an acute abdomen, and with adequate diagnostic procedures this diagnosis is usually obvious. However, a number of VEGF tyrosine kinase inhibitors have also been found to induce various degrees of abdominal discomfort or pain. Whether these symptoms must always be considered as preceding a perforation remains unknown, but it is obvious that meticulous and repeated examination of a patient treated with an angiogenesis inhibitor complaining from abdominal pain is mandatory. In a patient treated with an angiogenesis inhibitor in whom a perforation has developed, it is obvious that further treatment is absolutely contraindicated.

4.4. *Voice changes*

A number of VEGF inhibiting angiogenesis inhibitors such as VEGF-trap, AG–013736, BAY 57–9352, KRN951 and SU11248 have been associated with hoarseness in a number of patients. Hoarseness is a descriptive diagnosis with a wide variety of potential underlying mechanisms such as functional dysphonia, vocal cord paresis or paralysis, reflux laryngitis, Reincke's edema, laryngeal papillomas and vocal nodes.

It is conceivable that, as a result of the suggested physiological role of VEGF in mucosal integrity, VEGF inhibition could lead to local mucositis or laryngitis as underlying cause for this complaint. Whether VEGF plays another physiological role in the structure or function of the vocal cord or laryngeal region is largely unknown, and a particular role of VEGF in the physiology of the recurrent laryngeal nerve also remains speculative. Apart from one publication relating strong expression of VEGF-A mRNA in the squamous epithelium of papillomas and strong expression of VEGFR-1 and VEGFR-2 in the endothelial cells of the underlying vessels in pediatric patients with recurrent respiratory papillomatosis, a disease leading to hoarseness, no publications that might shed light into the possible relationship between the use of angiogenesis inhibitors and hoarseness are available.[29] As hypothyroidism often is accompanied by voice changes, and this disease has been described to be related to angiogenesis inhibition (vide infra), a possible causal relation can be considered.

With regard to diagnosis and treatment of hoarseness, it is our personal experience in a number of patients that local examination of the laryngeal region and vocal cord performed by an ear-nose-throat specialist did not demonstrate recognizable macroscopic or functional abnormalities. Any underlying oesophagitis was not assessed but was not clinically suspected. This is in line with the observations made with AG–013736 where hoarseness also was not related to cutaneous or mucosal toxicity.[30]

In patients complaining of hoarseness, continuation of antiangiogenic treatment usually does not lead to further progression of this complaint, whereas in all patients in whom treatment was stopped hoarseness disappeared in a number of weeks. When hypothyroidism as underlying cause for hoarseness is diagnosed, appropriate treatment of course is mandatory.

4.5. *Mucositis, gastrointestinal and skin toxicity*

VEGF plays a role in maintaining mucosal homeostasis and mucosal epithelialization after mucosal damage, and therefore it is conceivable that VEGF inhibition can result in mucosal damage leading to cutaneous toxicity, and upper or lower digestive tract mucositis with pain, vomiting or diarrhea.[28,31] The observation from preclinical models of experimental colitis that local application of basic fibroblast growth factor (bFGF) improved the outcome of the disease under study,

and the observation that prophylactic administration of oral VEGF is protecting against gastric damage induced by ethanol in rats, underscores the potential therapeutic as well as prophylactic role of proangiogenic factors in mucosal homeostasis.[32,33] However, as increased levels of VEGF are often found in chronic inflammatory bowel disease, it is also conceivable that, on the contrary, VEGF induces or maintains an inflammatory response.[34,35] Therefore the exact underlying mechanism of the (usually mild) cutaneous rash, mucositis, nausea, vomiting and diarrhea that are relatively often seen with the use of angiogenesis inhibitors remains somewhat unclear.

Looking at the frequency of any drug induced mucosal toxicity, there is a striking difference between tyrosine kinase inhibitors and VEGF antibodies. Whether the higher frequency of toxicity observed with tyrosine kinase inhibitors is the result of local VEGF suppression in the digestive mucosa following oral administration remains speculative but definitely cannot be ruled out. It is also conceivable that inhibition of other kinases such as the epidermal growth factor tyrosine kinase contributes to this phenomenon.

Clinical management of these side-effects usually includes conventional methods consisting of supportive care or pharmacologic treatment. If these strategies fail, however, treatment interruption or discontinuation could be indicated.

4.6. *Fatigue*

Although fatigue is a common complaint in patients with advanced cancer, the administration of angiogenesis inhibitors, both antibodies and small molecules, is associated with the occurrence of fatigue or an increase in its intensity. Myelosuppression, in particular the development of anemia, is not a frequently reported side-effect of VEGF targeting agents and therefore is not considered to be a frequent cause of treatment related fatigue, and other drug induced organ dysfunctions such as renal or adrenergic failure also don't seem to play a substantial causal role. However, before any mere supportive treatment is considered for fatigue as such, these factors have to have been looked for and corrected if appropriate. Although in phase I studies with some tyrosine kinase inhibitors fatigue has been found to be dose limiting, in most patients treatment induced fatigue is mild to moderate and has only infrequently been a reason for treatment interruption or dose reduction.

An important treatable cause of fatigue is hypothyroidism, which has recently been found to occur in up to 50% of patients treated with SU11248 or sunitinib.[36–38] Considering this new information, it is conceivable that also in patients being treated with any of the other tyrosine kinase inhibitors or with an antibody, fatigue or even more specifically the combination of fatigue and such typical complaints as skin changes, voice changes, constipation or other abdominal complaints, should urge the investigation of thyroid function and the initiation of appropriate treatment when indicated. Whether inhibition of VEGF, which plays a role in normal thyroid physiology, or the inhibition of RET kinase, which plays an important role in the development of thyroid cancer and is specifically inhibited by SU11248 and Bay 43–9006 or sorafenib, explains the onset of thyroid dysfunction and subsequent fatigue has not yet been fully clarified.[39–41] Of note here is the fact that increased serum levels of VEGF have been found in patients with Graves' disease, making a functional relation between VEGF and thyroid function plausible.[42]

4.7. *Transaminase elevations*

Although not elucidated in detail, it is well known that VEGF plays a role in structural and functional integrity of the liver. Although preclinical models of ischemia and reperfusion induced hepatic toxicity have shown seemingly conflicting data with regard to VEGF (and anti-VEGF substances) effects under these circumstances, models of chemically induced hepatitis or partial hepatectomy effects have more consistently shown growth stimulating, regenerative and cytoprotective effects of VEGF and a VEGFR agonist.[43–48] Therefore it is probably not unexpected that VEGF inhibiting agents, both tyrosine kinase inhibitors and antibodies have been found to induce transaminase elevations and sometimes dose limiting hepatotoxicity. Whether under these conditions transaminase elevations are due to a direct effect of the agent on hepatocytes, possibly partly due to inhibition of the epidermal growth factor receptor or due to an effect on endothelial cells of small hepatic blood vessels is not fully clear. From the clinical perspective, transaminase elevations fortunately almost always have been found to be reversible. Any grade three or higher transaminase elevation, of course is an urgent indication for treatment interruption and careful observation and should prompt a decrease in the dose of the inducing agent when prolonged treatment is to be considered.

4.8. *Neurological complications*

Apart from thromboembolic or bleeding complications, neurological complications such as seizures, dizziness and ataxia have been observed in conjunction with various tyrosine kinase inhibitors.[17,49,50] Whether these side-effects should be attributed to abnormalities in small blood vessel structure or function, resulting in cerebral ischemia, or whether a direct toxic effect on neuronal integrity plays a role remains to be determined. It is a well known fact, however, that a direct neuroprotective effect of VEGF through various different mechanisms has been suggested.[51–53] To date it seems that the neurological complications mentioned above have not been observed in association with the use of the antibodies targeting VEGF or VEGFR, which possibly could be explained by the fact that these larger molecules are not able to cross the blood brain barrier and therefore cannot inhibit VEGF activity in the central nervous system.

4.9. *Hand Foot Syndrome*

The hand-foot syndrome or palmar plantar erythrodysesthesia (PPE) is a painful erythema, often preceded by paresthesia that is a toxic reaction most often related to some cytotoxic agents like doxorubicin, docetaxel, and fluorouracil /capecitabine.[54] Histologically, PPE shows few specific findings, and the exact pathophysiology remains to be determined. Although some VEGF tyrosine kinase inhibitors have been found to induce this syndrome, the majority of agents from this class, as well as the antibodies targeting VEGF are not associated with

this side-effect. As VEGF has, as mentioned, physiological roles to play in mucosal integrity and neuronal functioning, it is conceivable that inhibiting VEGF could induce a 'combined deficit' that translates into this side-effect. As only a limited number of drug induced cases of PPE have been reported, it is not possible to give evidence based guidelines with regard to treatment, but the usual considerations such as withdrawal or dose reduction of the implicated drug can give amelioration of the symptoms. Apart from this, supportive treatments such as topical wound care, elevation, and cold compresses may help to relieve the pain if treatment is to be continued. Other methods that have been described are the use of systemic corticosteroids, pyridoxine (vitamin B6), blood flow reduction, Vitamin E and topical 99% dimethyl-sulfoxide.[55] Reports have been published that consider any of these measures as preventive measures when drugs with a strong association with PPE are going to be administered. To date, there is no rationale to advocate any of these measures when VEGF inhibiting angiogenesis inhibitors will be administered.

4.10. *Myelosuppression*

VEGF plays a role in both erythropoiesis and myelopoiesis, and therefore it is conceivable that myelosuppression could be a result of exposure to VEGFR targeting angiogenesis inhibitors. Indeed neutropenia and thrombocytopenia have been described as side-effects related to various tyrosine kinase inhibitors, most notably for the broad spectrum tyrosine kinase inhibitors sorafenib and sunitinib. These agents both block more than just angiogenic factors, and both hit Kit, the receptor for the stem-cell factor.

Whether myelosuppression should be attributed to inhibitory activity of these kinases remains to be elucidated.

5. Conclusion

Angiogenesis inhibitors targeting VEGF or VEGFR are among the largest group of anticancer agents that are currently being explored in clinical studies. Studies have clearly shown that these agents can be given safely to patients, and that they exert anticancer activity in a wide variety of tumor types when given either as single agent or in combination with cytotoxic chemotherapy. Currently, standard first line treatment for metastatic colorectal cancer almost obligatory includes the use of bevacizumab, whereas treatment options for metastatic renal cell cancer have significantly improved with the introduction and approval of the VEGF tyrosine kinase inhibitors sunitinib and sorafenib.

It is to be expected that in the near future a rapidly increasing number of patients will be exposed to any of these agents, and it is also very likely that an increasing number of studies will explore safety and efficacy of new derivatives that are currently becoming available.

The recent years have taught us that angiogenesis inhibitors are not completely devoid of toxicity, but share a recognizable pattern of side-effects. Most of these effects are clearly attributable to the inhibition of VEGF and VEGFR activity, and the observation and recognition of these side-effects have greatly increased our knowledge about the extensive physiological activity of VEGF. Although fatal side-effects due to the exposure to some of these agents have occurred, and other serious and sometimes life-threatening side-effects have lead to withdrawal of development of some other agents, we nowadays can consider both monoclonal antibodies to VEGF(R) and VEGF tyrosine kinase inhibitors to be manageable and safe as well as active anticancer agents. In the next years new toxicity data will definitely emerge in parallel with new efficacy data, but it is our personal conviction that in addition to the currently registered angiogenesis inhibitors, many more agents will turn out to be manageable, safe and efficacious, expanding treatment opportunities for large groups of cancer patients.

Conflict of interest statement

The authors indicate no conflict of interest

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