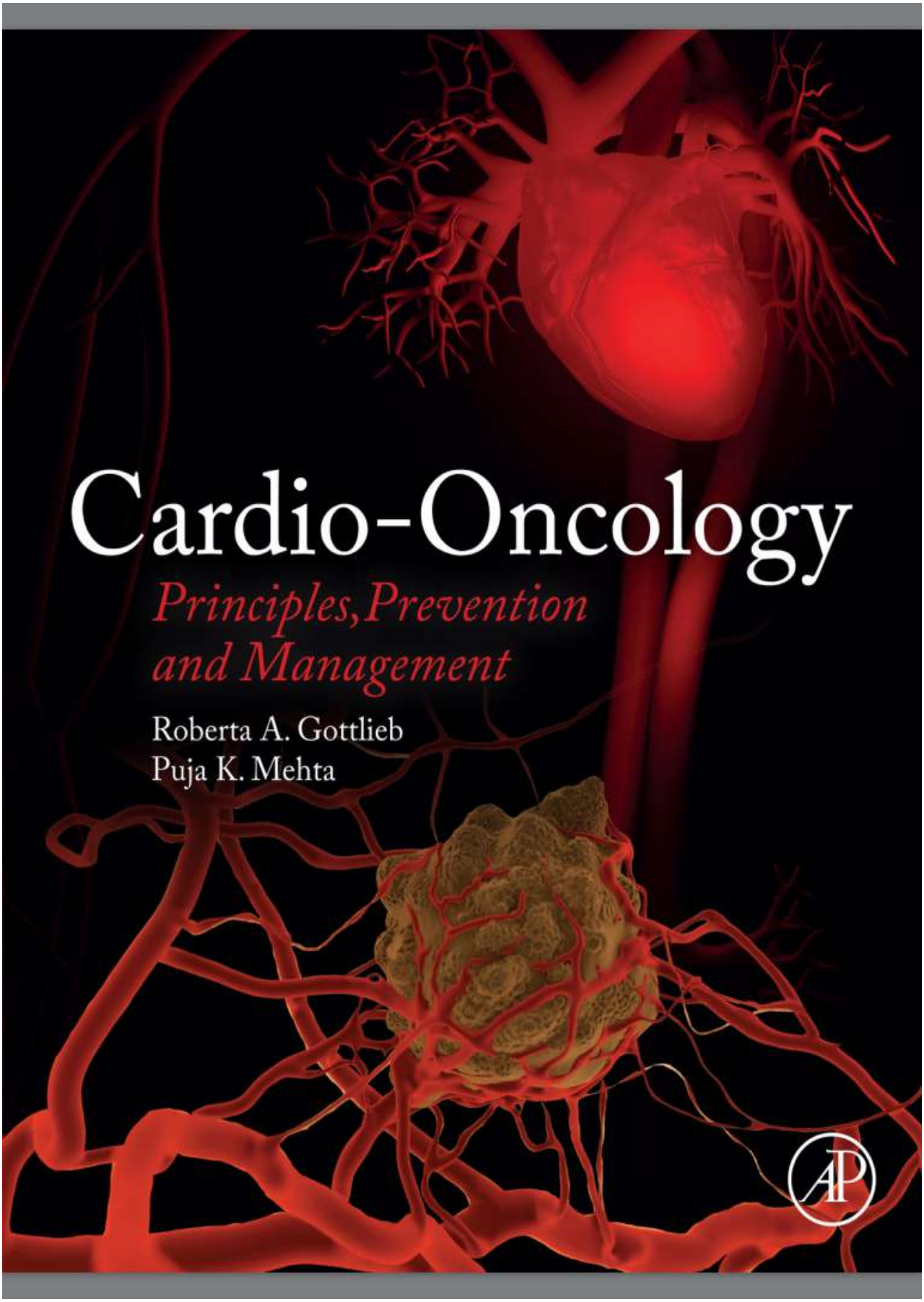
Cardio-Oncology
Principles, Prevention and Management
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Chapter 5

Cardiotoxic Effects of Anti-VEGFR Tyrosine Kinase Inhibitors

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INTRODUCTION

The bloodstream is essential to deliver oxygen and nutrients to the tissues and remove catabolites through endothelial cells of vessels. New vessels are important for the growth and development of tissues. Experiments conducted since the mid-1950s revealed that tumors stimulated endothelial cells to become highly active from a resting state. As in physiological settings, the formation of new vessels is fundamental for growth of the tissue or tumor. Angiogenesis is driven by the tumor in a sort of mutualistic relationship. This evidence led to Judah Folkman's idea of blocking the process of vascularization, which he called "antiangiogenesis" in order to limit tumor growth. This opened up a new research field [1–6]. Over the years, control of the angiogenic process has become an important therapeutic target. Antiangiogenic therapy supports the action of old therapies, such as chemotherapy and radiotherapy, and in some cases exceeds their limits. Two main types of molecules have been developed. These are monoclonal antibodies (such as bevacizumab and ramucirumab) and tyrosine kinase inhibitors (TKIs) (such as sorafenib, sunitinib, regorafenib, etc.). Another molecule has been developed acting as VEGF-trap. It is aflibercept [7–13].

In this chapter we will discuss about the biology of VEGF and its pathway, and will also focus on how TKIs act in cells and how they lead to cardiotoxic side effects.

ANGIOGENESIS: A TWO-EDGED SWORD

Development of new blood vessels from pre-existing blood vessels is called angiogenesis and is a normal physiologic process, particularly during the development of the embryo and fetus, and in adults during the ovarian cycle and in wound healing. Angiogenesis is the product of the balance between proangiogenic factors and antiangiogenic factors. Proangiogenic factors promote angiogenesis and comprise two categories: classical and nonclassical factors. Classical factors are vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), angiopoietins (Ang), insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), which are *basic*FGF (*b*FGF also called FGF-2) and *acidic*FGF (*a*FGF also called FGF-1), tumor necrosis factor (TNF), interleukins (ILs), in particular IL-6 and IL-8, transforming growth factor-α (TGF-α) and TGF-β. Nonclassical factors are stem-cell factor (SCF), tryptase and chymase. Antiangiogenic factors inhibit angiogenesis and comprise two categories: matrix-derived and non-matrix-derived factors. Matrix-derived factors are arresten, canstatin, endorepellin, endostatin, thrombospondins (TSPs): TSP-1 and TSP-2, tumstatin. Non-matrix-derived factors are interferons (INFs), interleukins (ILs, e.g. IL-4 and IL-12), angiostatin, chondromodulin I, tissue inhibitors of matrix metalloproteinases (TIMPs), soluble Fms-like tyrosine kinase 1 (sFlt-1), platelet factor-4, troponin I, and vasostatin (Fig. 5.1) [14–29].

Conditions such as blood-vessel constriction or obstruction, or systemic hypoxia (e.g., due to lung disease or high altitude) stimulate production of proangiogenic factors which attempt to compensate for the deficit through the production of new blood vessels. Hypoxia-inducible factor-1 (HIF-1), in the cytosol, is the key regulator of oxygen homeostasis. HIF-1 is constituted by two subunits α and β. HIF-1β is an aryl hydrocarbon nuclear receptor translocator (ARNT). The two subunits α and β possess basic helix–loop–helix (bHLH) and PER–ARNT–SIM homology (PAS) domains in their amino-terminal half, which are required for heterodimerization. The subunits α and β are part of a transcription factor family. In normoxic conditions HIF-1α is hydroxylated by prolyl hydroxylase enzymes (PHDs) on proline residues in the position 402 and 564, which are located within

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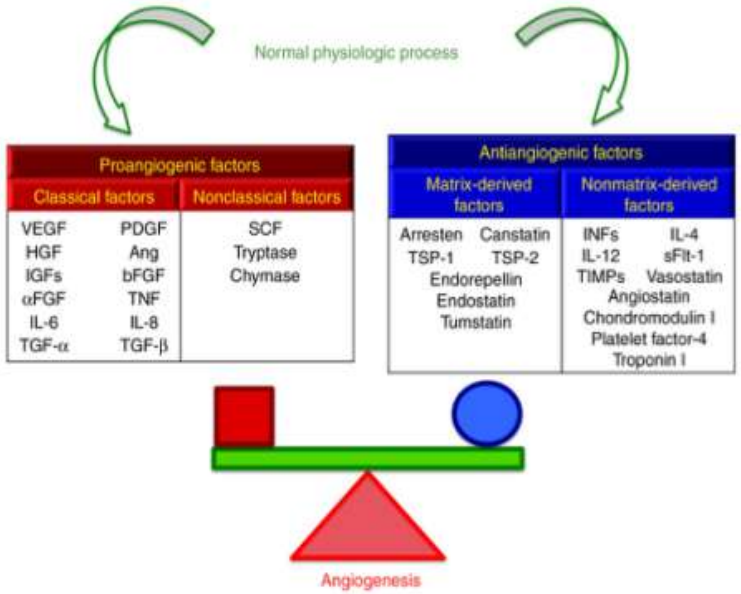

FIGURE 5.1 **The angiogenic process is the result of the equilibrium between proangiogenic factors and antiangiogenic factors.**

ODDD (O_2-dependent degradation domain). This hydroxylation determines the interaction with the von Hippel–Lindau (VHL) E3 ligase complex which results in ubiquitination of HIF-1α, leading to its proteasomal degradation. On the other hand, in hypoxic conditions there is a reduction in the quantity of substrates and coactivators of hydroxylation, such as O_2, Fe(II), and 2-oxoglutarate resulting in a decrease of HIF-1α hydroxylation and its accumulation in the cytosol. HIF-1α is then translocated to the nucleus, where HIF-1β is constitutively present. The interaction of coactivators, such as CBP/p300, with the two domains C-TAD and N-TAD on the C-terminus of the protein HIF-1α, helps the dimer HIF-1α/β for DNA binding on hypoxia response elements (HREs) and for the subsequent transcriptional activation. HREs are located within O_2-regulated genes. The transcription of target genes by HIF-1 includes angiogenic and hematopoietic growth factors, glycolytic enzymes, and glucose transporters. Among them, there is, for example, erythropoietin (EPO), which is necessary for red-blood-cell production. The production of erythrocytes increases the transport of oxygen to tissues so as to reach O_2 homeostasis. Other transcriptional products are endothelin-1 (ET-1), glucose transporter 1 and 3, IGF-II, nitric oxide synthase 2 (NOS2), VEGF and VEGF receptor FLT-1. HIF-α is a member of a family which also includes HIF-2α, also known as EPAS (endothelial PAS protein), and HIF-3α, also called IPAS (inhibitory PAS). HIF-2α is present in endothelium, lung, and cartilage. HIF-3α acts as a dominant negative inhibitor of HIF-1α DNA binding [30–34].

The transcription of target genes by HIF-1 leads to the production of several molecules, importantly including VEGF. The increased production of VEGF and other proangiogenic factors stimulate the creation of new vessels. VEGF isoforms interact with their receptors, VEGFRs, which are tyrosine kinases present on endothelial cell membranes. The interaction of VEGF with VEGFR activates an intracellular signal transduction pathway promoting survival, proliferation, and migration of the endothelial cells and tube formation. Angiogenesis consists of multiple processes: (1) endothelial cell division. Under the stimulus of proangiogenic factors endothelial cells become highly active. They have a significant mitotic index and develop the capability to migrate and disrupt the extracellular matrix (including tight junctions and gap junctions). (2) Pre-existing basement membrane rupture. (3) Endothelial cell migration. Endothelial cells invade the perivascular tissue, where they further proliferate. (4) New basement membrane development. (5) Tube formation. (6) Pericyte recruitment.

At first the growing tumor is in balance with blood supply and all cells receive sufficient nutrients and oxygen. However, as the tumor grows, it outstrips the blood supply needed for continued growth. The hypoxic tumor cells produce proangiogenic factors (e.g., VEGF) in excess of ambient antiangiogenic factors, so angiogenesis is triggered. These cells also interact by autocrine and paracrine pathways. The excessive cell growth and production of growth factors produce an uncontrolled angiogenesis, which result in a chaotic microvascular bed with ineffective blood flow

and regions of hypoxia. A vicious cycle is created that facilitates tumor growth and metastasis [35–42].

VASCULAR ENDOTHELIAL GROWTH FACTOR AND VEGFR SIGNALING PATHWAY

VEGF family members include VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). Among them, the most important one is VEGF-A, which has at least six splice variants ($VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{183}$, $VEGF_{189}$, and $VEGF_{206}$). The most common isoform contains 165 amino acid residues ($VEGF_{165}$). Each of these growth factor isoforms interacts with VEGF receptors on endothelial cells to activate them and to start the angiogenic process. VEGFRs are a family of homodimeric tyrosine kinase receptors that include VEGFR1, VEGFR2, and VEGFR3. VEGFR1 and VEGFR2 are involved in vascular angiogenesis and VEGFR1 can transphosphorylate VEGFR2. Besides, between these two, VEGFR2 has a major part in angiogenesis. VEGFR3 features lymphangiogenesis and it does not interact with VEGF-A. When VEGF is secreted, it binds to VEGFR, triggering homodimerization and autophosphorylation, thus allowing the activation of several cytoplasmic signaling molecules. There are two main signaling cascade pathways, which start from VEGF/VEGFR interaction: the RAS–RAF–MEK–ERK pathway and phosphatidylinositol-3-kinase (PI3K)/PTEN/Akt pathway. These signaling pathways lead to the transcription of genes involved in proliferation and survival of pre-existing endothelial cells. The first pathway is called the MAPK cascade. It starts from RAS, which is part of the protein family of small GTPases. RAS isoforms are KRAS, NRAS, and HRAS. When activated, RAS changes its state from the inactive form with GDP bound to the active form which binds GTP. There is a conformational switch, which facilitates its binding to RAF, the first kinase of the pathway. RAF is a serine/threonine kinase, with three isoforms [ARAF, BRAF, and CRAF (this last one also called Raf-1)]. Activated RAS recruits RAF to the membrane and activates it. RAF in turn phosphorylates and stimulates the kinase MEK, which activates the kinase ERK through phosphorylation. Lastly ERK phosphorylates several molecules, which include other kinases and transcription factors. This sequential activation of molecules starts various cellular phenomena linked to cell-cycle progression, cell proliferation or differentiation, protein translation and evasion from cell death related to the intensity and time duration of the signal.

The second pathway is the PI3K/PTEN/Akt pathway, which induces cell growth and survival. PI3K is the starting point of the cascade. It is possible to distinguish three classes of PI3Ks in correlation with structure and function, of which class IA is the main class involved in cancer. Class IA PI3Ks are initiated through receptor tyrosine kinases (RTKs) by growth factors (such as VEGF). Class IA PI3Ks are heterodimers composed by two parts: a regulatory subunit, p85, and a catalytic subunit, p110. When the p85 regulatory subunit interacts with the phosphotyrosine residues on RTKs or adaptors or activated Ras, it releases p110 to the plasma membrane where it phosphorylates phosphatidylinositol 4,5-bisphosphate (PI [4,5] P2) on the 3′OH position, generating PI(3,4,5)P3. PIP3 attracts phosphoinositide-dependent kinase 1(PDK1) and Akt, so that PDK1 phosphorylates Akt at threonine 308, thereby activating it. Activated Akt moves from cell membrane to cytoplasm to phosphorylate intracellular substrates but it also moves to the nucleus. It activates various regulators involved in transcription, such as CREB, E2F, and nuclear factor κB (NF-κB). Normally NF-κB is constitutively inhibited in the cytoplasm by IκB (inhibitory κ B protein kinase). When NF-κB is activated, it translocates to the nucleus where it stimulates the expression of several target genes governing cell proliferation, invasion, and inflammation. Thus, Akt has a part in survival, invasion, metastasis, cell cycle progression, migration, senescence, drug resistance, and DNA damage repair. Akt favors cell survival through the phosphorylation and inhibition of proapoptotic Bcl-2 family members and Mdm2, involved in p53-mediated apoptosis. Akt also inhibits the tuberous sclerosis complex-2 (TSC2) gene product tuberin by phosphorylating it. Tuberin is normally bound to hamartin, which is the product of TSC1. Tuberin is a GTPase-activating protein and consequently it is an inhibitor of the Ras-like small G protein Rheb. When TSC2 is phosphorylated, Rheb is activated which in turn activates the mammalian target of rapamycin (mTOR)—containing protein complex mTORC1. This activated complex on one hand triggers the p70 ribosomal S6 kinase (S6K1), whereas on the other hand inhibits the elongation-initiation factor 4E binding protein-1 (4E-BP1) through phosphorylation. These events lead to increased protein synthesis resulting in cell growth. The S6K through a feedback mechanism limits PI3K activation. It also inhibits the adaptor protein insulin receptor substrate 1, which is involved in insulin and IGF-1-mediated PI3K activation. Another mTOR complex mTORC2, phosphorylates Akt on serine 473 [43–50].

MECHANISMS OF ACTION OF TYROSINE KINASE INHIBITORS TARGETING VEGFR

The study of the VEGF/VEGFR pathway revealed the central role of this pathway in angiogenesis and led to the development of various drugs designed to inhibit it. The present-day armamentarium includes antibodies targeting VEGF and/or VEGFRs, soluble VEGF receptors, or receptor hybrids. Additionally there are TKIs that selectively target one or more than one VEGFR. TKIs have been developed to target not only VEGF receptors but also other targets, not only earning the name of "multikinase" inhibitors but also giving rise

TABLE 5.1 Molecular Targets of Anti-VEGFR Tyrosine Kinase Inhibitors

	Molecular Target												
Drug	VEGFR-1	VEGFR-2	VEGFR-3	PDGFRα	PDGFRβ	c-KIT	FLT3	CSF1R	RET	Raf-1	BRAF	TIE2	FGFR1
Sunitinib	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Sorafenib		✓	✓	✓	✓	✓	✓			✓	✓		
Regorafenib	✓	✓	✓		✓	✓			✓	✓	✓	✓	✓
Axitinib	✓	✓	✓										
Nintedanib	✓	✓	✓	✓	✓		✓		✓				✓
Vandetanib	✓	✓	✓		✓				✓				
Pazopanib	✓	✓	✓	✓	✓	✓							✓
Vatalanib	✓	✓	✓	✓		✓							
Cediranib	✓	✓	✓	✓	✓	✓							✓
Cabozantinib	✓	✓	✓			✓	✓		✓			✓	
Lenvatinib	✓	✓	✓	✓		✓			✓				✓
Linifanib	✓	✓	✓	✓	✓								
Telatinib		✓	✓		✓								
Brivanib	✓	✓	✓										✓
Foretinib	✓	✓	✓	✓	✓	✓	✓					✓	
Motesanib	✓	✓	✓	✓	✓	✓							
Lucitanib	✓	✓	✓	✓	✓								✓
Fruquintinib	✓	✓	✓										
Tivozanib	✓	✓	✓										
Apatinib		✓											

to off-target toxicity (Table 5.1). For example, regorafenib and sorafenib also inhibit RAF-1, B-RAF, PDGF receptor-β (PDGFRβ), and c-KIT. In particular, drugs targeting both VEGFRs and PDGFRs carry out inhibition on two fronts, blocking VEGFR on endothelial cells and PDGFR on pericytes as well as on VEGFRs expressed in tumor cells. TKIs affect not only tumor vasculature but also normal vasculature, which explains the cardiovascular toxicity evinced by this class of drugs. Acting on tumor vasculature they limit tumor growth and metastasis. TKIs mainly inhibit the tyrosine kinase activity of the receptor thus blocking the transmission of the signal after the interaction between VEGF and its receptor VEGFR. VEGF signaling promotes several cell functions, including cell survival and migration. Blockade of the receptor suppresses tumor cell survival, migration, and invasion [49,51,52].

CARDIOTOXIC EFFECTS BY ANTIANGIOGENIC DRUGS

TKIs act both on tumor and normal cells, thus leading to side effects including hypertension, renal vascular injury, and heart failure (HF). The cardiovascular side effects involve HF, hypertension, coronary artery vasospasm, and acute coronary syndrome, QT interval prolongation, asymptomatic or less commonly, symptomatic reduction of left ventricular ejection fraction (LVEF), and acute myocardial infarction (MI). It is possible to differentiate two types of toxicity, on-target toxicity, and off-target toxicity. In the first one, the toxicity is target related, which means that the kinase inhibited by the TKI carries out a crucial role in heart or vasculature. This cannot be overcome by developing more specific inhibitory molecules. Off-target toxicity is due to the fact that TKIs are multikinase inhibitors limited in their selectivity. Thus if the drug inhibits a kinase that is unrelated to tumor cytotoxicity but plays a role in cardiovascular function, off-target toxicity would develop. An example of off-target toxicity is the inhibition of AMPK (AMP-activated protein kinase) by sunitinib, an inhibitor of VEGFRs, PDGFRs, and c-KIT. AMPK has an important role in the metabolic homeostasis of the heart through regulation of energy stress. It is activated if the level of energy is decreased in the cardiomyocyte resulting in an increase in AMP levels. After activation, AMPK inhibits the energy-consuming pathways such as protein and fatty acid synthesis, and it stimulates the production

of energy by activating fatty acid oxidation and glycolysis. The inhibition by sunitinib has opposite effects because the energy consuming pathways are not suppressed and activation of energy-generating pathways is limited. This state of energy depletion paves the way to the activation of apoptosis (including mitochondrial membrane depolarization and cytochrome *c* release). Studies have demonstrated that there is myocardial cell loss by this drug which may be due to AMPK inhibition as well as loss of survival signals through VEGFR, PDGFR, and c-KIT [49,53–55].

The most frequent cardiovascular complication is hypertension, which is tightly linked to VEGF/VEGFR pathway inhibition. Indeed the increase in blood pressure is closely related to the treatment scheme, with hypertension occurring during cycles of drug administration and regressing between cycles. The interaction between VEGF and VEGFR2 activates the receptor, signaling through Src, PI3K, and phospholipase C (PLC), resulting in conversion of PIP2 to PIP3 by PI3K. PIP3 and PD1K activate Akt which in turn induces endothelial nitric oxide synthase (eNOS) to produce nitric oxide (NO). The activated enzyme PLC otherwise converts PIP2 to inositol trisphosphate (IP3) and diacylglycerol. IP3 is a second messenger which promotes Ca^{2+} influx into the cell, which also contributes to stimulate eNOS activity to produce NO. The latter activates guanylyl cyclase, increasing cGMP which leads to vasodilation, limits platelet aggregation, and suppressed growth of smooth muscle cells. Thus when TKIs inhibit signal transduction the final effect is a remarkable reduction in NO synthesis, resulting in vasoconstriction (thus hypertension) and endothelial dysfunction (microvascular impairment). These considerations are confirmed by the evidence that reduced VEGF-A production contributes to HF due in part to modified microvascular growth and reduced capillary density. Normally, VEGF helps to mitigate hypertension, but anti-VEGF therapy compromises this effect. Uncontrolled hypertension contributes to left ventricular hypertrophy; pathologic cardiac remodeling is characterized by cardiomyocyte hypertrophy that is not matched by an increase in capillary density. Studies in animal models indeed demonstrated an impairment in microvascular density, thinned ventricular walls, and lowered contractile function after deletion of the VEGF gene. These conditions favor the evolution from myocardial hypertrophy to HF, even though there are also other factors such as impaired calcium homeostasis in cardiomyocytes, interstitial fibrosis, and changes in energy metabolism. It has to be noted that the reduction in NO production not only determines vasoconstriction and endothelial dysfunction but also alters renal sodium handling, which supports in the long term the persistence of hypertension and renovascular injury.

Studies revealed that sunitinib plays a role in regulating ET-1 levels in blood. The increment in ET-1 quantity indicates that ET pathway is important in TKI-induced hypertension development. The VEGF/VEGFR interruption alters the equilibrium between NO and ET-1, facilitating vasoconstriction. ET-1 induces vasoconstriction through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the production of reactive oxygen radicals. Vasoconstriction facilitates hypertension. Another concurrent factor in maintaining hypertension in the long term is thyroid dysfunction. It has been reported that TKIs can cause hypothyroidism detected by a rise in TSH levels. Regardless of the etiology of the hypertension, it is important to control it with antihypertensives [49,56].

PDGF is an important glycoprotein that acts as a growth factor in various cell types. Among these cell types are smooth muscle cells, stromal cells, cardiomyocytes, and endothelial cells. The two PDGF receptors (α and β) are present in cells that have an oncogenic potential, contributing to the growth of gastrointestinal stromal tumor (GIST), glioblastoma, and chronic myelomonocytic leukemia. A study by Edelberg et al. revealed that PDGF mediates the interaction between cardiomyocytes and endothelial cells nearby. This interaction sustains angiogenesis and endothelial function, an interaction that is impaired in aged heart tissue. Deletion of the gene for PDGFRβ in cardiomyocytes results in impaired adjustment to afterload stress accompanied by a decrease in cardiac capillary density and consequently local tissue hypoxia. These processes contribute to pathologic remodeling characterized by ventricular hypertrophy and chamber dilation culminating in HF. Thus HF is the result of two combined effects. On the one hand the impairment in the production of NO causes hypertension, which is responsible for afterload stress of the heart. On the other hand the suppression of PDGFRβ limits the normal capacity to adapt to afterload stress. A recent study of sunitinib showed that the drug reduces the number of pericytes in the coronary microcirculation, thereby altering coronary microvasculature and further contributing to local tissue hypoxia, which underlies cardiac dysfunction [49,57,58].

Another important cardiovascular adverse event due to TKIs is thromboembolism. The interaction of VEGF with VEGFR activates the MAPK pathway and upregulates the prosurvival factor Bcl-2 in endothelial cells. The related protein Bcl-x_L, is an antiapoptotic factor that upregulates VEGF-A production in endothelial cells and in platelets and contributes to microvascular stability. VEGF-A/VEGFR2 also regulates the expression of proteins of the intercellular junctional complexes. VEGF-A modifies the endothelial cell through the increase of vascular permeability, upregulation of urokinase, tissue plasminogen activator, and the vascular-cell-adhesion molecule (VCAM). The three major isoforms of VEGF-A are present in megakaryocytes and platelets and are released during thrombin stimulation. Platelet activating factor (PAF), which is a proinflammatory molecule, stimulates the expression of VEGF-A by endothelial cells. VEGF released by cells activates VEGFR2 via autocrine and paracrine signaling. The paracrine pathway

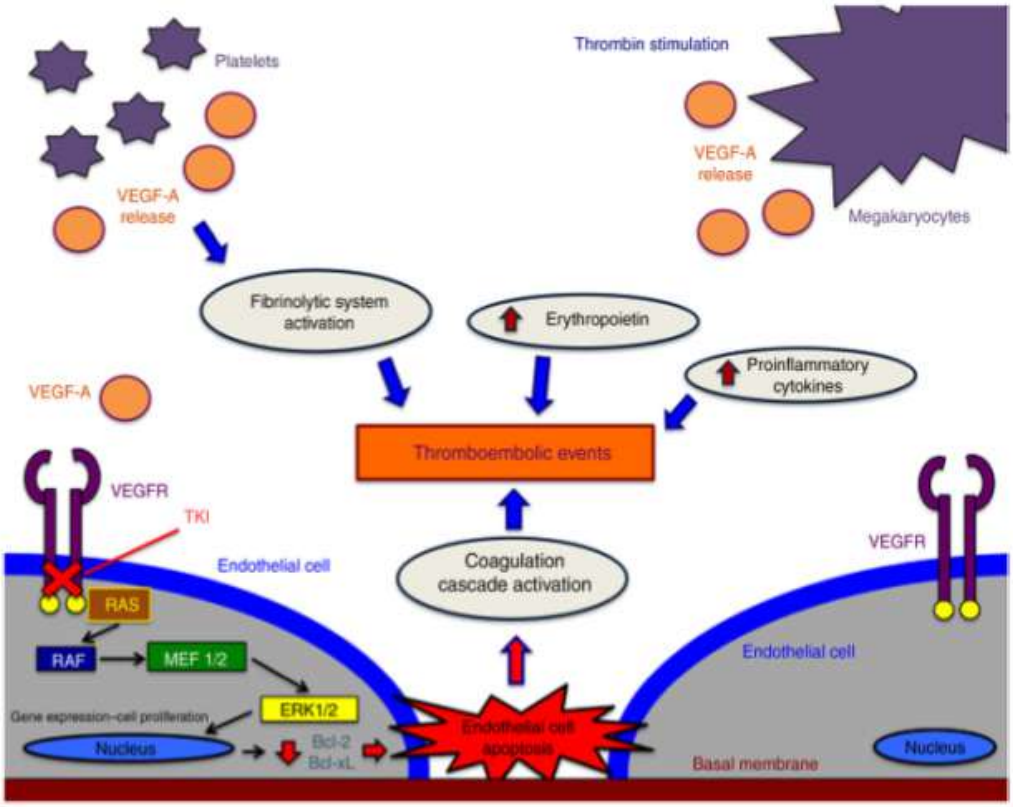

FIGURE 5.2 **Factors contributing to thromboembolism during TKI therapy.**

supports vascular permeability in abnormal conditions such as inflammation, and is therefore crucial for angiogenesis in cancer and inflammation. The VEGFR blockage during TKI therapy lowers Bcl-x_L and Bcl-2 levels, leading to apoptosis. Endothelial cell apoptosis exposes the subendothelial basement membrane, activating the coagulation cascade and paving the way for thromboembolic events. Furthermore, platelets release VEGF, which activates the fibrinolytic system, further contributing to thromboembolic events. VEGF is not only implicated in the production of NO by the endothelium but also in the production of PGI2, the reduction of which contributes to thrombosis, having an antiplatelet activity. The suppression of VEGF activity determines a consequential inversely proportional increase of EPO, which is responsible for the increase in hematocrit and blood viscosity, further contributing to the prothrombotic state. Elevated levels of proinflammatory cytokines also expose the patient to a higher risk of thrombosis (Fig. 5.2). Finally, the tumor itself contributes to the prothrombotic state through the release of procoagulant factors in response to TKI therapy [49,59].

ANTI-VEGFR TYROSINE KINASE INHIBITORS

Sunitinib

Sunitinib is a small orally administered multitarget inhibitor of tyrosine kinase receptors that carries out its anticancer activity on different targets that regulate angiogenesis, survival, and cell proliferation including VEGFRs 1-3, PDGFRα and PDGFRβ, c-KIT, FMS-like tyrosine kinase-3 (FLT3), CFS-1 receptor (CSF1R), and the product of the human RET gene (RET).

At present sunitinib is used for the treatment of various neoplasms such as unresectable GIST [60,61] and unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors [57]. In all these trials sunitinib demonstrated a cardiotoxicity profile peculiar enough to be further evaluated. Although sunitinib is a generally well-tolerated medication, hypertension is the most common side effect with a grade >2 hypertension risk ratio (RR) of 23 compared to placebo, as shown by a meta-analysis of approximately 5000

patients. Rini et al. further demonstrated that this adverse event required a dose adjustment or the addition of a drug in 6.8% of cases and that sunitinib is associated with a higher incidence of left ventricular dysfunction than other TKIs. Cardiac involvement was confirmed by an observational study in which Schmidinger et al. reported an increased incidence of cardiac event defined as elevated cardiac enzymes, symptomatic arrhythmia requiring treatment, new left ventricular dysfunction, or acute coronary syndrome in one third of patients treated with sunitinib. In another observational study, Schmidinger et al. reported that patients with advanced renal cancer receiving chemotherapy with sunitinib or sorafenib developed a higher incidence of cardiovascular events and, in particular, 40.5% of them registered ECG rhythm changes including conduction disturbances, axis change, QRS amplitude changes, ST segment depression, and elevation, T wave changes and QT prolongation; 18% of these were symptomatic, with clinical symptoms such as angina, dyspnea, and dizziness. Subsequently, many of these patients developed reduced LVEF, regional contractile dysfunctions, relaxation disturbances greater than grade 1, and pericardial effusion. In the GIST setting, researchers have documented an increased incidence of cardiovascular events. Chu et al. reported in patients with GIST previously treated with imatinib, that sunitinib treatment caused cardiac events in 11% of patients, with reductions in LVEF ≥15%, and increased blood pressure > G2 in 17% of patients. The authors also noted that many of the patients treated with sunitinib or sorafenib exhibited in an increase of cardiac biomarkers such as creatine kinase myocardial band (CK-MB; 54.5% vs. 78.6%) and troponins (54.5% vs. 21.4%) [56–58,60–64].

Sorafenib

Sorafenib is an orally administered multitarget small molecule inhibitor of tyrosine and serine/threonine kinases including VEGFR2 VEGFR3, PDGFRα and PDGFRβ, c-KIT, FLT3, v-raf-1 murine leukemia viral oncogene homolog 1 (RAF1) including BRAF kinases. This molecule is currently approved for the treatment of various cancers and in particular advanced hepatocellular carcinoma Child-Pugh Class A or B and advanced renal-cell carcinoma (RCC).

Sorafenib was evaluated by Llovet et al. in a phase-III randomized controlled trial in which it was compared against placebo in two cohorts of patients with advanced HCC never treated with chemotherapy. Sorafenib showed a significant benefit in terms of overall survival and a good profile of cardiovascular tolerability (fatigue >G2 4% vs. 3%; blood pressure >G2 2% vs. 1%). Cardiac ischemia or infarction occurred in 3% versus 1% of patients. Cardiac events were also reported in another phase-III randomized trial by Cheng et al. in which the incidence of heart attack or cardiac ischemia occurring during treatment was 2.7% in sorafenib-treated patients and 1.3% in the placebo-treated group.

In another randomized controlled phase-III trial sorafenib was compared with placebo for the treatment of previously treated metastatic RCC demonstrating a significant benefit in terms of overall survival. The increased incidence of cardiovascular toxicity (fatigue >G2 14% vs. 5%; blood pressure >G2 4% vs. 0%) was similar to that recorded in the expanded access cohort of 2504 patients (blood pressure >G2 5%). Subsequent retrospective analysis showed that the increase in pressure was predictive of tumor response to treatment with sorafenib. Escudier et al. reported 22 events of myocardial ischemia (4.9% vs. 1.4%) and CHF (1.7% vs. 0.7%) among patients treated with sorafenib versus placebo. They also attributed an increase of the QT/QTc interval with consequent alteration of ventricular repolarization to sorafenib. In conclusion, sorafenib is a well-tolerated drug with a cardiotoxicity profile associated with higher incidence of hypertension (usually well controlled with a standard antihypertensive therapy), cardiac ischemia and infarction, with a higher risk for thromboembolic events (RR 3.03) as showed by a meta-analysis of more than 10,000 patients [65–69].

Regorafenib

Regorafenib is an oral multikinase inhibitor with a triple mechanism of action against targets involved in the regulation of angiogenesis, cell proliferation, and tumor stroma, including VEGFR1-3, TIE2, FGFR1 and PDGFRβ, c-KIT, and RET, along with the intracellular signaling kinases c-RAF/RAF-1, and its BRAF V600E mutant. Regorafenib is currently indicated for the treatment of refractory advanced colorectal cancer and advanced GIST resistant to imatinib and sunitinib chemotherapies. Like the other TKIs, regorafenib has a cardiotoxic profile. A recent meta-analysis assessed the risk of hypertension in patients taking regorafenib and reported a RR of hypertension >G2 of 8.39 and an incidence of hypertension >G2 of 12.5%. The authors point out that the overall incidence of hypertension differs significantly on the basis of the type of pathology (56.1% among patients with GIST, 49.0% among patients with RCC, 27.8% among patients with metastatic colorectal cancer, and 36.1% among patients with hepatocellular carcinoma). The incidence was highest with GIST and lowest with RCC, but it was clinically manageable with treatment interruption or dose reduction. Of note, in the randomized controlled phase-III GRID trial, authors reported one patient with cardiac arrest. Regorafenib was also studied in metastatic colorectal cancer in two large phase-III randomized controlled trial, the CORRECT trial and the CONCUR trial (the first on a western population and the second on an Asian population). Hypertension >G2 was reported in 7%

and 11%, whereas fatigue >G2 was reported in 9% and 3%, respectively. Furthermore, in the CONCUR study, 1 patient had an atrial fibrillation, 1 patient had mesenteric ischemia, and 1 patient had dyspnea, whereas in the CORRECT trial, authors reported all-grade dyspnea in 6% and nosebleeds in 7% of patients [70–72].

Axitinib

Axitinib is a third-generation selective inhibitor of VEGF receptors 1–3 and is indicated for the treatment of patients with advanced renal cancer after failure of prior treatment with sunitinib or a cytokine. Axitinib also has a cardiovascular toxicity profile revealed by the various trials in which it was evaluated. Axitinib is associated with a significant increase in cases of hypertension, as demonstrated by a recent meta-analysis of Abdel-Rahman where the subgroup of patients treated with Axitinib had a RR of hypertension (all grades) of 2.63; this value is not significantly different from the other drugs studied in this analysis (sunitinib RR 3.48; cediranib RR 2.26). In contrast, treatment with sunitinib significantly increased the risk of bleeding (sunitinib RR 2.80 vs. axitinib RR 1.02 vs. cediranib RR 1.11) and venous thromboembolism (sunitinib RR 2.05 vs. axitinib RR 0.53 vs. cediranib RR 0.51). There was no subgroup analysis of arterial hypertension >G2 but this information can be extrapolated from the analysis of outcomes of individual trials reported in the meta-analysis (axitinib 15.5% vs. 5.5% in controls). No information on high-grade left-ventricular dysfunction was reported. The cardiovascular profile of axitinib was also investigated in another meta-analysis by Qi et al. which included trials involving various tumors (metastatic RCC, metastatic melanoma, metastatic breast cancer, advanced non-small-cell lung cancer (NSCLC), pancreatic cancer, and all histological subtypes of advanced thyroid cancer), although the majority of cases were renal and pancreatic advanced neoplasms. The reported incidence of all grades hypertension was 40.1% (RR 3.00), whereas the incidence of hypertension >G2 was 13.1% (RR 1.71) and was associated with treatment interruption or reduction of the dose of the drug. Furthermore, the increase in the incidence of all grades of hypertension was greater in patients with renal neoplasms (57.6%) compared to other neoplasms (28.4%), which was also the case for hypertension >G2 (28.4% vs. 7.2%). Finally in a recent analysis of the phase-III AXIS published by Rini et al. in which axitinib was compared with sorafenib, the authors reported an incidence of 40% for hypertension of all degrees and 16% for hypertension >G2 (trial not blinded); the causes for drug discontinuation were fatigue (1%; 4) and transient ischemic attack (<1%; 3). Further analysis also revealed a relationship between diastolic blood pressure > or equal to 90 mmHg and tumor response: thus hypertension may not only predict efficacy of treatment with axitinib but also suggests that antitumor effect and cardiovascular toxicity may be inseparable [73–76].

Nintedanib

Nintedanib is a novel oral selective TKI against all subtypes of VEGF, FGF and PDGFRα and β, together with RET and FLT3. Nintedanib is usually very well tolerated, with a favorable cardiovascular safety profile tested in various neoplastic diseases including RCC, HCC, ovarian/endometrial cancer, lung cancer, breast cancer, prostate cancer, gliomas, and colorectal cancer. In a phase-II trial in advanced renal neoplasms, Eisen et al. reported that nintedanib, unlike other TKI molecules, does not give rise to QTc interval prolongations. Furthermore, cardiovascular adverse events were not encountered. Nintedanib has been studied as a single agent and in association with chemotherapeutic regimens, with the best results in the treatment of advanced lung and ovarian cancers. Nintedanib was investigated in the LUME-Lung 1 phase-III, randomized, double-blind trial, which compared nintedanib plus docetaxel versus docetaxel plus placebo in patients with locally advanced/metastatic non-small-cell lung cancer after failure of first-line therapy. The most common adverse events in patients in the experimental arm included diarrhea responsive to supportive care and reversible elevation of liver enzymes managed with dose reduction. Furthermore, the only reported cardiac adverse event was hypertension <G2 in 15.4% of the patients. Recently du Bois et al. reported their experience in patients suffering from advanced ovarian cancer and treated upfront with a standard first-line chemotherapy regimen containing carboplatin and paclitaxel plus nintedanib or placebo. In this randomized phase-III trial the most common adverse events were gastrointestinal too; in particular, diarrhea >G2 had an incidence of almost 22% in nintedanib arm versus 2% in the placebo arm. Drug-related adverse events leading to death occurred in three patients in the nintedanib group but none of these was correlated to cardiovascular events (diarrhea, kidney failure, and peritonitis) [77,78].

Vandetanib

Vandetanib is another oral small molecule TKI with multitarget action against receptors including VEGFR1, VEGFR2, VEGFR3, EGFR, RET, PDGFRβ. This drug has been approved for the treatment of advanced medullary thyroid cancer and has also been studied in the treatment of advanced NSCLC. This drug has a cardiotoxic profile like the other TKIs and has been the subject of several meta-analyses. Zang et al. analyzed alterations of the QTc interval in patients with neoplasms and treated with vandetanib and observed a 3.7% incidence of high-grade prolonged QTc interval in patients with nonthyroid cancers and 12.0% in patients with medullary thyroid cancer. A

subsequent meta-analysis of W-X Qi et al. included 11 trials and more than 3000 patients with advanced NSCLC and advanced thyroid cancer; they reported an increased incidence of hypertension >G2 in patients with lung cancer (7.6%, RR 10.22) and thyroid cancer (8.8%), but incidence was lower in patients with other neoplasms (3.4%). This suggests that incidence of hypertension may be significantly influenced by the type of neoplasia. This suggests that all patients receiving vandetanib should be monitored for hypertension, and in cases of severe or persistent hypertension despite the initiation of antihypertensive treatment, dose reduction or interruption may be necessary. The risk of developing high blood pressure in patients with advanced NSCLC was also the subject of a recent meta-analysis performed by Y. Liu et al., in which the authors showed that vandetanib compared to control was responsible for a significant increase in the risk of hypertension (RR 5.58) and prolongation of QTc interval (RR 7.90). Cardiovascular toxicity may be underestimated in the first-line treatment due to the small amount of data from only two studies; further studies are needed to define the risk of patients in this setting [79–81].

Pazopanib

Pazopanib is another multitarget oral TKI that exerts its action against VEGFR1, VEGFR2, VEGFR3, PDGFRα and β, FGFR1, FGFR3, c-KIT, LCK, and macrophage colony-stimulating factor-1 receptor. It is currently available for treatment of patients with advanced renal cancer and soft-tissue sarcomas, although it has also been studied in advanced epithelial ovarian cancer.

Like the other TKIs, pazopanib has a particular cardiovascular toxicity profile that has been evaluated in detail by WX Qi et al. in a meta-analysis of the major studies, which showed that pazopanib significantly increased the risk of high blood pressure >G2 (RR 2.87) with an incidence of 6.8% among patients with advanced RCC and 6.2% among other malignancies without statistically significant differences between the groups; it was associated with an increase in morbidity and interruption of chemotherapic treatment. Pazopanib is also responsible for abnormal ventricular repolarization. AM Pick et al. in their review recommended a close monitoring of ECG and cardiac enzymes in patients with existing heart disorders or QT prolongation, due to an increased incidence of torsades de pointes (less than 2%); they recommended avoiding other drugs with direct action on the same cardiac phase. The same authors point out that Pazopanib is also associated with thromboembolic events with an incidence of MI and cerebrovascular accidents of about 3% versus 0% in placebo group. These data were similar to those of another study about ovarian cancers in which CN Sternberg et al. reported an increased incidence of cardiovascular events (MI/ischemia 2%, cerebrovascular accident <1%, and transient ischemic attack <1% compared with the none reported in the placebo arm). In treatment of advanced soft tissue sarcomas (PALETTE trial), pazopanib was associated with increased incidence of fatigue (fatigue >G2 13%) and hypertension (>G2 7%) with a significant reduction in LVEF compared with placebo (5% vs. 3%) [82–84].

Vatalanib

Vatalanib is a small molecule TKI that interferes with the ATP-binding site of VEGFR1-3, with an inhibitory action also against c-KIT and PDGFRα. The safety profile of vatalanib has been evaluated in several malignancies although larger studies were performed in the treatment of metastatic colorectal cancer and in advanced NSCLC. In colorectal cancer, vatalanib was evaluated in two randomized phase-III trials. In the CONFIRM 1 study, previously untreated metastatic colorectal cancer patients were randomly assigned to receive FOLFOX chemotherapic regimen plus valatanib or placebo. The authors reported a significant increase in cardiovascular toxicity >G2 among patients assigned to the experimental treatment compared to placebo (hypertension 23.0% vs. 6.8%, pulmonary embolism 5.7% vs. 1.7%, with no significant difference in venous thromboembolism incidence (5.2% vs. 3.5%). In the study CONFIRM 2, patients with advanced colorectal neoplasm whose disease had recurred or progressed during or within 6 months of treatment with irinotecan in combination with fluoropyrimidine were randomly assigned to a FOLFOX chemotherapic regimen plus vatalanib or placebo. The cardiac toxicity profile reported by the authors was very similar to that reported in the CONFIRM 1 trial and in particular they noted an increase in >G2 hypertension (21.8% vs. 6.0%) and fatigue (14.7% vs. 7.4%). In vatalanib arm, there was also a higher incidence of deep vein thrombosis, pulmonary embolism, and thromboembolic events. Vatalanib was evaluated in an uncontrolled phase-II trial in patients with NSCLC (stage IIIB or IV) who had disease progression on a first-line platinum-containing or chemoradiotherapy regimen. They reported an incidence of hypertension >G2 of 12%, fatigue >G2 of 2% and pulmonary embolism >G2 of 6%; two patients died from causes probably related to the treatment (pulmonary hemorrhage) [85–87].

Cediranib

Cediranib is an indole–ether quinazoline molecule and a potent small TKI, orally taken. It is a pan-VEGF receptor TKI (VEGFR-1, VEGFR-2, VEGFR-3), with greater selectivity for VEGFR-2; it also inhibits PDGFRs (PDGFRα, PDGFRβ) and c-KIT. Studies revealed that this molecule has an IC_{50} of <0.001 μM for VEGFR2, <0.003 μM for VEGFR3, <0.002 μM for c-KIT, <0.005 μM for PDGFRβ,

<0.036 μM for PDGFRα, and <0.026 μM for FGFR-1. It has been studied in patients with recurrent glioblastoma that failed standard therapy, in epithelial ovarian cancer combined with platinum-based chemotherapy, in advanced biliary tract cancer, in NSCLC, in colon cancer, breast cancer, metastatic renal cancer, and hormone-refractory prostate cancer. Hypertension and fatigue are the main side effects reported. The Recentin in Glioblastoma Alone and With Lomustine (REGAL) study is a randomized, phase-III, placebo-controlled, partially blinded study evaluating the efficacy of cediranib in monotherapy or in combination with lomustine versus lomustine alone in 325 patients with recurrent glioblastoma who previously received radiation and temozolomide. They were assigned 2:2:1 to receive cediranib (30 mg) in monotherapy, cediranib (20 mg) plus lomustine (110 mg/m^2), or lomustine (110 mg/m^2) plus placebo. Among grade 3 and 4 adverse events the authors noted hypertension and pulmonary embolism. Hypertension was present in 18 patients (14.1%) receiving cediranib alone, but occurred in only 8 patients (6.5%) receiving cediranib plus lomustine. No G > 2 hypertension was encountered in the group placebo plus lomustine. Pulmonary embolism occurred in four patients (3.1%) with cediranib, in six patients (4.9%) receiving cediranib plus lomustine, and in four patients (6.3%) in the group receiving placebo plus lomustine. Unfortunately the study did not satisfy the primary end point of demonstrating a benefit in progression-free survival for either cediranib-containing arm versus lomustine, even though preclinical studies suggested synergistic activity of anti-VEGF therapy in combination with radiation. For this reason cediranib has been studied in combination with chemoradiotherapy in a phase-II trial. A randomized, open-label, phase-II study recruited 90 women with measurable platinum-sensitive, relapsed, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer, and women with deleterious germline BRCA1/2 mutations. They were divided in two groups: 46 women received olaparib 400 mg twice daily, whereas 44 received the combination of cediranib 30 mg daily and olaparib 200 mg twice daily. The most common G > 2 side effects were fatigue, diarrhea, and hypertension. Incidence of these adverse events was higher in the cediranib plus olaparib group, confirming the phase-I findings. No hypertension was observed in the olaparib group. In the cediranib plus olaparib group, hypertension of varying severity was encountered: G1, two patients (5%), G1-2, fifteen patients (34%), G3, seventeen patients (39%), and G4, one patient (2%). Fatigue of grade 2–3 was increased about twofold in the group cediranib plus olaparib in comparison with the olaparib group (54% vs. 26%). Another phase-II study evaluated the use of cediranib in this group of cancers. Of 23 women who received the drug at a dose of 45 mg, 10 patients (43%) had grade-1–2 hypertension, 8 patients (35%) had grade 3, whereas 2 patients (9%) had grade-4 hypertension. Eleven patients (48%) had grade-1–2 fatigue and seven patients (30%) had grade-3 fatigue. Two patients (9%) had grade-1–2 chest pain and two patients (9%) had grade-4 myocardial ischemia. In the same study 51 patients were treated with cediranib at the dose of 30 mg, among them 22 patients (43%) had grade-1–2 hypertension, 14 patients (27%) had grade-3 hypertension, whereas no grade-4 hypertension was reported. Fatigue (grade 1–2) was reported in 26 patients (51%) and grade 3 in 10 patients (20%). Three patients (6%) had grade-1–2 chest pain. Different results were reported in a placebo-controlled, randomized, double-blind phase-II trial of patients with metastatic carcinoma or who developed metastatic disease or local pelvic recurrence after radical treatment. Sixty-nine patients received carboplatin AUC of 5 plus paclitaxel 175 mg/m^2 by infusion every 3 weeks for a maximum of six cycles with cediranib 20 mg or placebo orally once daily until disease progression. Among the 34 patients receiving standard chemotherapy plus cediranib grade-1/2 hypertension was present in 19 patients (59%); no grade 3 or 4 was reported. Dyspnea grade 1/2 was present in 4 patients (13%), whereas no grade 3 or 4 was noted. Fatigue grade 1/2 was present in 26 patients (81%), grade 3 in 4 patients (13%), with no grade 4 fatigue. A randomized, double-blind, placebo-controlled phase-III trial (ICON 6, NCT00532194) compared cediranib versus placebo in combination with carboplatin and paclitaxel in platinum-sensitive recurrent ovarian cancer patients. In this study 456 women were randomly assigned to receive standard therapy with carboplatin and paclitaxel plus placebo followed by placebo as maintenance therapy, or carboplatin and paclitaxel plus cediranib 20 mg/day followed by placebo as maintenance therapy or cediranib 20 mg/day as maintenance therapy. In this study grade-3 hypertension was encountered in 4 patients (7%). A recent multicenter, placebo-controlled, randomized phase II trial of 124 patients with histologically confirmed or cytologically confirmed advanced biliary tract cancer were treated with first-line cisplatin and gemcitabine chemotherapy (25 mg/m^2 cisplatin and 1000 mg/m^2 gemcitabine, on days 1 and 8 every 21 days, for up to eight cycles) with either 20 mg cediranib or placebo once a day until disease progression. Cediranib was received by 62 patients. Grade-1/2 fatigue was seen in 36 patients (58%) and grade-3/4 fatigue in 16 patients (26%) in the cediranib group. Grade-1/2 hypertension was present in 19 patients (31%), while grade 3/4 was present in 23 (37%). Fifteen patients (24%) had grade-1/2 dyspnea, whereas only one patient (2%) had grade-3/4 dyspnea. MI grade 3/4 occurred in one patient (2%). Unfortunately, cediranib did not enhance the progression-free survival of these patients. Ongoing phase-III trials are studying cediranib for the first-line treatment of metastatic colorectal cancer (mCRC). These are HORIZON II and HORIZON III. The HORIZON II trial compares chemotherapy (FOLFOX or XELOX) with cediranib or placebo in patients with

metastatic colorectal cancer, while the HORIZON III compares mFOLFOX6 (modified 5-fluorouracil [5-FU]/leucovorin/oxaliplatin) in combination with cediranib versus mFOLFOX6 in combination with bevacizumab. An open-labeled, single-agent, phase-II study evaluated the development of hypertension and proteinuria in 46 patients with recurrent epithelial ovarian carcinoma receiving cediranib. The authors reported a rapid onset of hypertension: by the third day of drug administration, 67% patients developed hypertension, 73% by day 7, and 87% by the end of the study. Grade-3 hypertension developed in 43% of patients, and 24% developed grade 3 fatigue [88–100].

Cabozantinib

Cabozantinib is a TKI approved for the treatment of patients with progressive, metastatic medullary thyroid cancer (mMTC). It has been also studied in advanced prostate cancer and advanced RCC. Studies revealed that it inhibits the activity of multiple kinases including RET, MET, VEGFR-1, -2 and -3, KIT, TRKB, FLT-3, AXL, and TIE-2. Elisei et al. conducted a double-blind, phase-III trial in which they compared cabozantinib (140 mg per day) to placebo in a 2:1 ratio in 330 patients with documented radiographic progression of mMTC. Among these patients, 219 were treated with cabozantinib. Common cardiovascular side effects in cabozantinib-treated patients included fatigue, hypertension, asthenia, and dyspnea. All grades fatigue was present in 86 patients (40.7%), with grade 3–4 in 20 patients (9.3%). All grades hypertension was present in 70 patients (32.7%), with grade 3–4 in 18 (8.4%). All grades asthenia was present in 45 patients (21%), with grade 3–4 in 12 (5.6%). All grades dyspnea was reported in 29 patients (13.6%), whereas grade 3–4 dyspnea occurred in 5 patients (2.3%). Severe adverse events were more frequent in cabozantinib-treated patients (214 patients). These included pulmonary embolism in 5 patients (2.3% vs. 0% in placebo group) and hypertension in 5 patients (2.3% vs 0%). Among the grade-5 adverse events which occurred within 30 days of last dose of cabozantinib, treatment-related events included respiratory failure, sudden death, and cardiopulmonary failure (total three patients). Cabozantinib (140 mg per day) in this study achieved a statistically significant enhancement of progression-free survival in these patients. In a phase-II study by Smith et al., 144 patients with chemotherapy-pretreated metastatic castration-resistant prostate cancer (mCRPC) received open-label cabozantinib; 93 patients received a daily dose of 100 mg, whereas the other 51 patients received 40 mg daily until tumor progression or intolerable toxicity. Cardiovascular side effects reported in the study were dose-related fatigue, dyspnea, hypertension, and pulmonary embolism. In the 100-mg cabozantinib cohort 77 patients (83%) had all grades fatigue, of which 25 patients (27%) presented grade 3–4 fatigue. All grades dyspnea was present in 30 patients (32%), of which 6 patients (6%) had grade 3–4 dyspnea. All grades hypertension was present in 23 patients (25%), of which 14 patients (15%) had grade 3–4 hypertension. In the 40-mg cabozantinib cohort 32 patients (63%) had all grades fatigue, of which 7 patients (14%) suffered grade 3–4 fatigue. All grades dyspnea was present in 13 patients (25%), of which one patient (2%) had grade 3–4 dyspnea. All grades hypertension was present in 10 patients (20%), of which 6 patients (12%) had grade 3–4 hypertension. Incidence of grade 3–4 pulmonary embolism was 8% in the 100-mg cohort, versus 18% in the 40-mg cohort. The study found that the drug exhibited significant clinical activity in mCRPC. Cabozantinib has also been studied in a randomized, open-label, phase-III trial, the METEOR trial, comparing the efficacy of cabozantinib to everolimus, in 658 patients with RCC and disease progression after VEGFR-targeted therapy. Patients received cabozantinib 60 mg daily (330 patients) or everolimus 10 mg daily. The cardiovascular side effects were fatigue, hypertension, asthenia, dyspnea and peripheral edema. All grades fatigue was present in 186 patients (56%), grade 3–4 fatigue was present in 30 (9%). All grades hypertension developed in 122 patients (37%), with grade 3–4 hypertension in 49 (15%). All grades asthenia occurred in 62 patients (19%), with grade 3–4 asthenia in 14 (4%). All grades dyspnea was present in 62 patients (19%), with grade 3–4 in 10 (3%). All grades peripheral edema was present in 31 patients (9%), with no grade 3 or 4. The study revealed longer progression-free survival in the cabozantinib group than in the everolimus group. Other studies showed that there was a higher incidence of thrombotic events using the drug in comparison with placebo. Venous thromboembolism showed an incidence of 6% versus 3% and arterial thromboembolism 2% versus 0%. The studies in patients with mMTC evaluated the effect of this drug on QTc interval. There was a mild increase in QTcF of 10–15 ms after four weeks of treatment, but none of the patients had a QTcF > 500 ms [101–104].

Lenvatinib

Lenvatinib, another TKI, inhibits mainly VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), but it also inhibits other kinases including FGF receptors FGFR1, 2, 3, and 4, PDGFRα, KIT, and RET. It has been approved for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. It has also been studied in advanced hepatocellular carcinoma and metastatic RCC.

The SELECT trial, a randomized, double-blind, multicenter phase-III study, evaluated 612 patients with progressive thyroid cancer refractory to iodine-131 treatment, of which 392 were randomized to receive lenvatinib at a dose of 24 mg per day in 28-day cycles (261 patients) or placebo (131 patients). The authors observed all grades

hypertension in 67.8% patients, with grade 3–4 hypertension in 41.8%. All grades fatigue or asthenia was present in 59%, with grade 3–4 in 9.2%. All grades peripheral edema occurred in 11.1%, grade 3–4 in 0.4%. All grades pulmonary embolism was present in 2.7%, with grade 3–4 in 2.7%. This study showed improvements with lenvatinib compared to placebo in progression-free survival and tumor response rate, although patients who received lenvatinib had more side effects. Recently Schlumberger et al. conducted a phase-II multicenter, open-label, single-arm trial in patients with medullary thyroid carcinoma. Lenvatinib was administered to 59 patients once a day at a starting dose of 24 mg in 28-day treatment cycles for eight cycles in the absence of disease progression, uncontrolled toxicities, or death. They reported all grades fatigue in 31 patients (53%), with grade 3–4 in 3 (5%). All grades hypertension was present in 30 patients (51%), of which 4 (7%) had grade 3–4. All grades dyspnea occurred in 16 patients (27%), of which one patient (2%) had grade 3–4. One patient (2%) interrupted treatment due to hypertension. Among serious adverse events that occurred in 51% of patients, pulmonary embolism occurred in 3.4%. Motzer et al. studied this drug in a randomized, phase-II, open-label, multicenter trial in advanced or metastatic clear-cell RCC, enrolling patients to receive lenvatinib plus everolimus or single-agent lenvatinib or single-agent everolimus. The treatment was taken once a day in 28-day continuous cycles. Patients received the single-agent therapy with lenvatinib 24 mg daily (two capsules of 10 mg and one capsule of 4 mg). Single-agent lenvatinib was received by 52 patients. Of these, 22 (42%) had grade 1–2 fatigue or asthenia, whereas 4 patients (8%) had grade-3 fatigue or asthenia; no grade 4 was reported. Grade 1–2 hypertension was present in 16 patients (31%), whereas 9 patients (17%) had grade-3 hypertension; no grade 4 was registered. Peripheral edema was present only grade 1–2 in eight patients (15%). Grade 1–2 dyspnea was experienced by 10 patients (19%); only one patient had grade-3 dyspnea (2%), and no patient developed grade-4 dyspnea. One patient receiving single-agent lenvatinib had a fatal MI [105–109].

Linifanib

Linifanib is another oral TKI drug. Its activity is selective for the VEGF and platelet-PDGF receptors, thereby blocking two of the most important signaling pathways involved in tumor progression. The activity and efficacy of linifanib has been studied in many tumors (NSCLC, renal cancer, hepatocellular cancer, colorectal cancer, and breast cancer). The major results were achieved in the field of advanced NSCLC. A prospective randomized phase-II study evaluated linifanib at two different doses (7.5 and 12.5 mg) versus placebo in combination with carboplatin and paclitaxel. The addition of linifanib significantly improved progression free survival (PFS) [5.2 months for placebo vs. 10.2 months (7.5 mg dose) or 8.3 months (12.5 mg dose)]. Both treatment arms containing linifanib authors reported an increased incidence of adverse events, the most common of which included diarrhea (27.7%), anemia (14.3%), and high blood pressure (4.3%); thrombocytopenia was the most frequent cause of treatment interruption and/or reduction of the associated chemotherapy regimen. The tolerability profile of linifanib was already investigated in previous phase-I studies. In particular, Chiu YL et al. conducted a careful study of linifanib's effects on cardiac ventricular repolarization. Although the study was small (24 patients, in a crossover design), they concluded that linifanib, unlike other TKI, does not cause an increased risk of QTc prolongation at the highest concentration for the maximum tolerated dose of the drug [110,111].

Telatinib

Telatinib is an orally active small molecule TKI with activity toward VEGFR2-3 and PDGFRβ. The activity of this molecule has been assessed in several kinds of cancer. Mross et al. published a multicenter phase-I study in which 29 heavily pretreated patients with advanced colorectal cancer were treated with telatinib at 600 up to 1500 mg twice daily showing that the molecule had a substantial effect on tumor shrinkage and also showed a favorable safety profile. High blood pressure was the most common adverse event (all grades, 36%, grade 3, 28%) but was clinically manageable with appropriate antihypertensive therapy, although in three patients it was necessary to reduce the dose, interrupt treatment, or discontinue treatment. Authors also observed fatigue (2% grade 1–2 in non-continuous dosing schedule, and 7% in the continuous dosing schedule) and diarrhea as specific toxicities requiring dose reduction or interruption of treatment. At the time of this writing, results of phase-II trials have not been published. One phase-II trial will evaluate telatinib in combination with chemotherapy in patients with advanced gastric cancer (NCT00952497) [112].

Brivanib

Much scientific evidence has also shown that among the factors responsible for angiogenesis, a key role belongs to the FGF. For this reason, new molecules were synthesized with the ability to selectively block VEGF and FGF simultaneously with the intent to overcome drug resistance to VEGF pathway inhibitors.

Brivanib is an oral dual inhibitor of the growth signals from the activation of VEGFR and FGFR that demonstrated a tenacious antitumor and antiangiogenic activity. This drug has been tested in several cancers including colorectal cancer, hepatocellular cancer, renal cell cancer, and NSCLC. A phase-I study demonstrated high activity of brivanib in solid tumors; the main toxicities of the drug

at the maximum tolerated dose (800 mg continuous, intermittent 800 mg, and 400 mg bid) consisted of nausea, diarrhea, fatigue (15–25% G3-4), dizziness, hypertension (15-25% G3-4), headache and anorexia; cardiac ventricular repolarization changes were not reported. Two randomized phase-III studies evaluated brivanib at 800 mg orally daily in advanced hepatocellular carcinoma. The study BRISK-FL is a noninferiority study that compared brivanib with the standard sorafenib in patients with advanced hepatocellular carcinoma without prior chemotherapy. The study BRISK-PS evaluated patients who progressed on/after or were intolerant to sorafenib that were randomly assigned (2:1) to receive brivanib 800 mg orally once per day plus best supportive care (BSC) or placebo plus BSC. Both studies failed to demonstrate any benefit in terms of overall survival and also reported a characteristic dose-dependent increase in the incidence of toxicities with brivanib (BRISK-FL fatigue >G2 14.5%; blood pressure >G2 13.3%—BRISK-PS fatigue >G2 13%; blood pressure >G2 16%) which were responsible for a decrease in performance status in patients assigned to brivanib. The authors of both studies report deaths that were considered possibly related to treatment in the experimental arm not clearly attributed to cardiovascular function abnormalities. Finally another randomized phase-III study investigated the efficacy of brivanib in combination with cetuximab (anti EGFR moAb) compared to single-agent cetuximab plus placebo in patients with chemotherapy-refractory advanced colorectal cancer. Authors did not demonstrate any significant benefit in terms of survival global but only in terms of progression free survival at the cost of a significant increase in related toxicity (fatigue >G2 25%; blood pressure >G2 11%; dyspnea >G2 8%) and a more rapid deterioration of patient performance status, terminating further experimental trials with this drug [113–117].

Foretinib

Foretinib is an oral multikinase inhibitor targeting MET, RON, AXL, Tie-2, VEGFR, c-KIT, Flt-3, and PDGFR signaling pathways.

Foretinib activity was evaluated in several preliminary studies where it was found to be particularly active against gastric and renal cancer. In particular MA Shah et al. studied Foretinib in a phase-II trial in which the drug was administered on an intermittent or daily schedule in a single cohort of unselected previously treated patients with advanced or metastatic gastric cancer. Although neither mode of drug administration caused significant toxicity, including the cardiovascular profile (fatigue >G2 4.2% and 3.8%; blood pressure >G2 6.3% and 15.4%), foretinib as a single agent did not show significant effect on tumor regression except for patients carrying a MET gene amplification. In another phase-II study, TK Choueiri et al. evaluated the activity of foretinib with the same intermittent or daily schedules in 74 patients with locally advanced, bilateral multifocal, or metastatic sporadic papillary RCC or known hereditary papillary RCC, and observed appreciable antitumor activity (overall response rate 13.5%), especially in the subgroup of patients carrying a germline mutation of the MET gene. Drug treatment was also associated with significant cardiovascular toxicity for both intermittent and daily regimens (blood pressure >G2 35.1% and 68%; fatigue >G2 5.4% and 8.0%; proteinuria >G2 5% and 5%). They also reported nine events of nonfatal pulmonary embolism of which three were only recognized at the time of disease progression [118,119].

Motesanib

Motesanib is an angiogenesis inhibitor that targets VEGFR1-3 and also exerts direct antitumor activity by acting as an antagonist PDGFR and c-KIT. Its chemical structure and mechanism of action make motesanib a very promising molecule against tumor-mediated angiogenesis. Motesanib has been evaluated in several phase-I and -II and preclinical trials, but in large phase-III randomized trials, it has not shown significant benefits on major clinical endpoints of overall survival or progression-free survival. In the phase-III randomized controlled MONET-1 study, GV Scagliotti et al. did not detect any improvement in overall survival and minimal cardiotoxicity comparing motesanib to placebo when used in combination with carboplatin and paclitaxel in patients with lung cancer, squamous cell non-small-cell stage IV. However, a preplanned analysis of an Asian subgroup conducted by Kubota et al. found encouraging results in terms of objective response rate, progression-free survival, and overall survival, providing a strong rationale for the phase-III randomized controlled MONET-A study among Asian patients in Japan, South Korea, Taiwan, and Hong Kong. This trial of 401 patients with Stage IV or recurrent nonsquamous NSCLC randomized patients in a 1:1 ratio to paclitaxel and carboplatin plus either placebo or motesanib. Although Motesanib exhibited no significant difference in cardiovascular toxicity >G2 between motesanib and placebo, the drug failed to demonstrate efficacy in terms of objective response rate, progression-free survival, and overall survival [120,121].

Lucitanib

Lucitanib is a newer oral FGFR1-2, VEGFR1-3, and PGFRα-β inhibitor, although preclinical proteomics analyses suggest it may exert its antitumor activity through additional unidentified targets. Lucitanib assessment in the clinical setting is still at a very preliminary stage. It has been tested in a single phase-I/IIa trial on solid tumors, showing promising results in terms of effectiveness (complete + partial response 26–50% depending on tumor subgroup) with a

maximum tolerated dose of 15 mg/day. Cardiovascular toxicity was frequently enountered including hypertension (all grades 91%; >G2 57.9%) requiring antihypertensive medication, dose reduction, or discontinuation, as well as asthenia (42%) and proteinuria (57%). Based on the preliminary findings of efficacy, lucitanib will be investigated in further trials (NCT02202746, NCT02053636) [122,123].

Fruquintinib

Fruquintinib is another recently-developed oral TKI which exerts its antitumor activity through the selective blocking of VEGFR1-3. Fruquintinib is still at an early stage in clinical trials. In a phase-Ib trial fruquintinib has shown good efficacy with a sufficient safety profile when used at 5 mg once daily dose in cycles of 3 weeks on and 1 week off in patients with previously treated advanced colorectal cancer. The most significant toxicities were hand–foot syndrome (HFS), hoarseness, proteinuria, hypertension, and fatigue (no incidence data are reported). Further studies are ongoing (NCT02415023, NCT02691299, NCT02314819) [124].

Tivozanib

Tivozanib is an oral TKI that selectively inhibits the signal transduction pathway activated by VEGFR1-3 receptors. Preclinical studies of tivozanib demonstrated activity on xenograft models of RCC and have justified its extensive testing in this clinical setting. Phase-I studies of Tivozanib at a dose of 1.5 mg/day for 4 weeks on and 2 weeks off reported promising clinical responses with side effects of arterial hypertension, fatigue, and headache. On the basis of these data, tivozanib was evaluated in a discontinuation phase-II randomized trial in patients with advanced RCC; the most common severe adverse event (G3-4) was hypertension (12%), and elevation of GGT (16%). Subsequently, tivozanib was evaluated in a large confirmatory phase-III randomized, controlled trial (TIVO-1) in which tivozanib 1.5 mg/day for 3 weeks on and 1 week off was compared with sorafenib 400 mg/day in patients with advanced RCC not previously treated with VEGF or mTOR inhibitors. Tivozanib study showed particular cardiovascular toxicity characterized by blood pressure >G2 in 27% (vs. 18% on the sorafenib arm) and from fatigue >G2 5% (vs. 4% with sorafenib). Hypertension was the leading cardiovascular cause dose reduction (2% vs. 4%). In tivozanib arm it should be noted that many deaths were associated with cardiovascular complications (two deaths resulted from myocardial infarction, two from cardiac failure, and one each from hypertension, dyspnea, cerebrovascular accident, aortic aneurysm rupture, coronary arteriosclerosis artery, cardiac arrest, apnea, pulmonary embolism), and for these reasons, in addition to the negative trend shown in median overall survival (28.8 vs. 29.3 months) and to the poor US study accrual (only 3%) the FDA denied permission to register this drug for this indication [125–127].

Apatinib

Apatinib is another oral TKI that acts by selective inhibition of VEGFR-2 signal transduction. The first studies that evaluated the antitumor activity in solid tumors demonstrated safety of apatinib at a dose of 500 mg/day. Experimentation with apatinib has been mainly in the field of gastric and breast cancer. X. Hu et al. evaluated apatinib in previously treated advanced non triple-negative breast neoplasm. The apatinib cardiovascular profile was very similar to that of other TKIs, with hypertension >G2 in 21.1%, with almost half of the patients requiring dose reduction. A similar experience was encountered in the triple negative patients at the same dose, with hypertension >G2 in 11.9% of patients in combination with fatigue >G2 in 3.4%. In this study, authors also reported one symptomatic pericardial effusion and one uncontrolled atrial fibrillation thought to be treatment related. Apatinib has shown promise in the treatment of advanced gastric cancer, where two schedules of administration were evaluated (850 mg daily vs. 425 mg twice daily) in a randomized controlled phase-II study in heavily pretreated patients. The cardiotoxicity profile was characterized by high blood pressure >G2 and fatigue >G2 similar in the two groups (8% vs. 11%; 2% vs. 2%), but showing a better overall safety profile when used in the schedule 425 mg twice daily [128–130].

CONCLUSIONS

The goal of this chapter is to provide to the reader a quick and useful guide regarding the use of TKIs in oncology with a focus on cardiovascular toxicity. To do this we have tried to collect all the data available in the literature, although some of the agents in this drug class are still at an early stage of experimentation. The TKIs exert their anticancer activity by inhibiting signal transduction of ligands and their receptors regulating tumor proliferation, its relationship with the microenvironment and particularly with angiogenesis. The angiogenesis mechanisms involve several key molecules such as VEGF and the corresponding receptor (VEGFR), whose action is crucial for the development and spread of solid tumors. It was amply demonstrated by preclinical studies that angiogenesis increases the metastatic potential of various malignancies such as hepatocellular carcinoma. The main TKIs studied in the antineoplastic field are sunitinib, sorafenib, regorafenib, axitinib, and pazopanib. They have proven to be effective in the treatment of various cancers such as colorectal, kidney, and liver. The management of adverse events related to the drug is crucial to increase the overall survival of patients maintaining a good quality of life. Surely, among the most important side effects, also in

consideration of the aforementioned mechanism of action, there are those of the cardiovascular type, which require dose reductions and/or discontinuation of treatment, thereby limiting their efficacy. The risk for a cardiovascular event is related to the underlying cardiovascular risk of the patient. Patients with pre-existing chronic disease such as hypertension, diabetes, renal disease, or previous cardiovascular event are considered at highest risk, so proactive management of these conditions is warranted before administering a TKI. As revealed by the pivotal clinical trials, the occurrence of a G3 type event, however rare, must necessarily result in a temporary interruption of the treatment and/or a reduction of 50% of the dose of the drug on the basis of individual tolerance. Among the main events reported in the trials include high blood pressure, the incidence of which is significantly different depending on the type of cancer (RCC vs. non-RCC 25.9% versus 20.4%, RR 1.27, 95% CI: 1.13-1:43, p <0.001), although patients with RCC may have higher blood pressure at the outset. For Sunitinib, RR was 8.20 for patients with RCC (95% CI: 4.70 to 14:29), and only 1.42 for patients with GIST (95% CI: 0.81 to 4.2). This may be related to the higher levels of VEGF found in patients with clear cell RCC due to loss of function in Von Hippel-Lindau (VHL), or more likely because of the increased rate of nephrectomies, with reduction of nephrons and glomerular filtration rate in patients with RCC responsible for a reduced urinary excretion of the drug and perhaps also impaired sodium clearance. The use of TKIs is responsible in turn for cardiac and renal damage. It was reported that high blood pressure was associated with reduction of left ventricular function during treatment with sunitinib in patients with RCC, although the mechanism is still unclear, and although it was not possible to exclude direct cardiotoxicity of the drug. Some authors postulate that ventricular dysfunction may depend on the direct action of the VEGF pathway causing an alteration of the vascular architecture responsible for a lower microvascular density and diminished production of NO. The treatment schedule influences the risk of developing high blood pressure. In particular, H. Zhu et al. showed in a meta-analysis that the continuous administration of TKIs has an increased risk of higher blood pressure than the intermittent schedule (RR 1:32, 95% CI: 1.18–1.48, $P < 0.001$), probably due to the unremitting action of the drug on the vasculature. With regard to kidney damage, it has been shown that this may arise from cardiovascular abnormalities. The TKIs can contribute to renal injury through hypertension as well as direct effects on VEGFR signaling in the renal tubules and glomeruli. While arterial hypertension is one of the most common challenges managing patients receiving TKIs, hypertension has also been recognized as a predictor of tumor response, suggesting that antitumor effects and cardiovascular side effects may be inseparable.

Management of patients receiving TKIs should nevertheless provide for close blood pressure monitoring and appropriate medical management of hypertension. Treatments may include the use of angiotensin converting enzyme (ACE) inhibitors or angiotension-II receptor blockers (ARBs) that have demonstrated antiangiogenic effects in xenograft models. Nondihydropyridine calcium channel blockers that induce secretion of VEGF should be avoided in preference to the dihydropyridines (amlodipine, nifedipine). Despite these suggestions, the best therapeutic approach is not fully established, and is further complicated by interactions between TKIs and antihypertensive agents, necessitating further studies. Some authors suggest avoiding drugs that interfere with the CYP3A4 because of the potential increase in TKI effect. Blood pressure control can also include diuretics, alpha blockers, and beta blockers, although most data are from studies using bevacizumab. The limits of interpretation of data about hypertension are numerous. First, many trials reported hypertension as values >150/100 mmHg or an increase of 20 mmHg rather than values >140/90 mmHg, and no randomized controlled trials were designed with the aim to standardize this measurement. In addition, baseline blood pressure was not always reported, although such information is essential in nephrectomized patients may already have secondary hypertension.

Cardiovascular toxicity should not, however, limit the use of these drugs, as they have demonstrated great utility in the treatment of some cancers such as RCC, which until recently had few or no medical treatment options. Several authors, having noted the correlation between high blood pressure (>140/90 mmHg) and tumor response, have suggested hypertension may predict efficacy and might be helpful in selecting subgroups of patients most likely to benefit from the therapy. Because of the increased risk of cardiovascular complications including end-stage heart disease in these patients, there is great interest in early detection of cardiovascular toxicity. Recently K.A. Bordun et al. recreated hypertension in mice treated with bevacizumab or sunitinib and showed that the echocardiographic assessment by tissue velocity imaging (TVI) could detect early LV systolic dysfunction before the appearance of abnormalities in conventional echocardiographic indices. Of course, much more needs to be done in the development of these techniques but these encouraging findings suggest that this approach may help to prevent more severe cardiovascular events [56,57,60,62,131–144].

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