International Journal of Cardiology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? What both cardiologist and oncologist should know about novel angiogenesis inhibitors

Elena Conti [a,*], Adriana Romiti [b], Maria Beatrice Musumeci [a], Jasmine Passerini [a], Luigi Zezza [a], Vittoria Mastromarino [a], Chiara D'Antonio [b], Paolo Marchetti [b], Francesco Paneni [c], Camillo Autore [a], Massimo Volpe [a,c]

[a] Cardiology, Department of Clinical and Molecular Medicine, Sapienza University of Rome, Ospedale Sant'Andrea, Rome, Italy
[b] Oncology, Department of Clinical and Molecular Medicine, Sapienza University of Rome, Ospedale Sant'Andrea, Rome, Italy
[c] IRCCS Neuromed Pozzilli, IS, Italy

ARTICLE INFO

Article history:
Received 15 November 2012
Accepted 18 January 2013
Available online xxxx

Keywords:
Acute coronary syndromes
Angiogenesis inhibitors
IGF-1
Growth factors
VEGF

ABSTRACT

We aimed to revise the increasingly accruing data about the association between anti-tyrosinkinase, "targeted" cancer drugs and the development of arterial thrombotic events or acute coronary syndromes. Further insights into the involved pathophysiologic mechanisms, and into the clinical implications are overviewed.
Antiangiogenesis has become a mainstream of cancer therapy, leading to development of a specific class of drugs. Besides, a "wider" angiogenesis network made up of several growth factors, can be recognized as target of a higher number of compounds. Their widespread use has been progressively favored over conventional chemotherapy, because of their better safety/efficacy profile, even allowing a prolonged administration. However, there is a growing awareness of an association between these useful drugs and serious cardiovascular side effects including myocardial infarction, stroke, heart failure and cardiovascular death, in addition to the known relation with the most frequent hypertension onset. Observational studies indeed report that combined cardiovascular events may reach figures of 20–40%, and, for their management, several monitoring, diagnostic and therapeutic regimens have been suggested.
On the basis of the available data we recommend an active screening program for acute coronary syndromes in the "at risk" period, immediately after the beginning of the "targeted" drug therapy, and during the whole administration time. Likewise, a mandatory cardiological specialistic evaluation is warranted to plan a schedule of follow-up evaluations for diagnostics, including ECG, echocardiogram, and multimarker evaluation. An appropriate treatment with antiplatelet or anticoagulant drugs, endothelial protective agents or cardiovascular interventions is similarly advised.

1. Introduction

Inhibition of tumor angiogenesis has become a recent major therapeutic advance in cancer therapy. It is realized by the so called "targeted" cancer drugs which inhibit a broad net of angiogenic factors, including vascular endothelial growth factor (VEGF) as the "proper" angiogenic mediator, insulin-like growth factor-1 (IGF-1) as the central angiogenic inducer, platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) as interplaying, ranked for power, angiogenic effectors (Fig. 1). In turn, angiogenic "wide" network itself is crucial to cardiovascular health [1] mainly due to its defending role against endothelial cell apoptosis which, induced by different threats, may modulate both atheroma development/complication and coagulation activation in cancer patients [2]. Anti-angiogenic-treated patients, while acquiring cancer cure, may thus become more susceptible to (athero) thrombosis [2]. Hence, besides hypertension as the most common side effect, they may also develop cardiac ischemia or infarction with a 2–3% incidence in randomized controlled trials [3] and meta-analyses [4], and even up to a 40% incidence in patients with a previous history of coronary artery disease in observational studies [5].

This brief review outlines the pharmacology of "targeted" drugs with a wide anti-angiogenic effect. Moreover, pathophysiology, clinical management and treatment of acute coronary syndromes (ACS), the most typical arterial thrombotic event (ATE) presumably linked to their administration, are revised.

* Corresponding author at: Intensive Cardiac Care Unit, Cardiology, Sapienza University of Rome, Ospedale Sant'Andrea, Via di Grottarossa 1035–1039, 00189, Rome, Italy. Tel.: +39 06 33775561; fax: +39 06 33775061.
E-mail address: elena.conti@uniroma1.it (E. Conti).

0167-5273/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2013.01.052

Key messages box

Summary of key information on pharmacology of TKI cancer drugs, pathophysiology behind, clinical relevance and proposed management of associated atherothrombotic side effects. ACE-I: angiotensin converting enzyme inhibitors; ACS: acute coronary syndromes; ATEs: arterial thrombotic events; BNP: brain natriuretic peptide; BP: blood pressure; CABG: coronary artery bypass graft; ECG: electrocardiogram; EF: ejection fraction; EGF: endothelial growth factor; EMP: endothelial microparticles; ESA: erythropoietin stimulating agents; FFAs: free fatty acids; GF: growth factors; GIST: gastrointestinal stromal tumor; HCC: hepatocarcinoma; HF: heart failure; HT: hypertension; ICD: implantable cardiverter defibrillator; IGF-1: insulin-like growth factor-1, IHD: ischemic heart disease; NSCLC: non small cells lung cancer; PDGF: platelet-derived growth factor; PLT: platelet-derived factor; PM: pace-maker; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitors; and VEGF: vascular endothelial growth factor.

Key messages box

Drugs, mechanisms, clinical features, diagnostics and therapeutics

Anticancer "targeted" drug use and mechanisms of action

Mainly used in lung, kidney, colorectal, breast, GIST, hepatocarcinoma, prostate and pancreatic cancers (Tables 1 and 2) [14,15], achieving relevant survival gains.

So-called "targeted" *TKIs* involved in counteracting a "wide" web of angiogenic factors [2,6] (Fig. 1) with some targeted drugs classifiable as "proper", other as "accidental" antiangiogenic therapies.

Angiogenesis inhibitors are relevant drugs in pathophysiological treatment of cancer, with potential cardiovascular side effects [1,2].

VEGF is the "proper" angiogenic mediator, *IGF-1* the central angiogenic inducer, *PDGF/EGF/cKIT* are interplaying, ranked for power, angiogenic effectors [2].

Pathophysiology of (coronary) atherothrombotic side effects

Early onset of atherothrombotic events after therapy initiation, with median time after drug beginning 7 months (2.5 if associated ESA) [2,31]).

Drug-induced endothelial apoptosis/damage is the pivotal step by which antiangiogenic drugs induce atheroma development/complication and associated ACS [1,2,4].

Concurrent/triggering mechanisms: cancer-related thrombogenicity, drug-induced HT promoting high shear-stress at plaque sites [1], malignant transformation with resulting increased prothrombotic apoptotic EMP [42,43,49], higher on-treatment PLT reactivity [47] and endothelial–PLT interactions [48].

Drug-damaged endothelium shifts its anticoagulant into procoagulant properties by exposing subendothelial tissue factor and von Willebrand factor [2,4,44] by increasing fibrin formation [51], by inducing complement activation and by sustaining vascular inflammation.

Leukocytosis [53] and cell free DNA (from cell lysis induced by inflammation and by anticancer drugs) cooperate to thrombosis [54], and may ease *autoimmune phenomena* (anti-phospholipid antibodies [55–58]) contributing to atherothrombosis.

Antiangiogenic drugs *hinder insulin anti-atherogenic actions* (glucose uptake, lipogenesis and antilipolysis) with ensuing thrombophilic hyperglycemic, atherogenic lipoproteins- & FFAs-rich environment prone to atherothrombosis [1] (everolimus and temsirolimus almost invariably associated with combined dyslipidemia [29] and hyperglycemia [28,29].

Individual variability in the effectiveness of growth factor network (variable serum levels or genetic background of IGF-1 or VEGF), finally accounts for the patient *susceptibility* to the efficacy of anticancer drugs or for his different *vulnerability* to their side effects [2,4].

Clinical incidence of (coronary) atherothrombosis early after TKI therapy

Randomized: *ACS* (1.5%) in lung cancer treated with bevacizumab vs paclitaxel/carboplatin [28].

Stroke (respectively 2% and 3%) and pulmonary embolism (2%) with everolimus and temsirolimus [29,30].

Threefold as *ATEs* (2%) in a sorafenib/sunitinib meta-analysis (> 10,000 patients) regardless of the type of malignancy or of TKI [3,4].

Myocardial ischemia and infarction in sorafenib-treated HCC (3%) [10] and RCC (4.9%) [10,31]. *Stroke* (1.5%) in sorafenib-treated RCC [31].

Cerebrovascular ischemia (2%), *HF* (1.6% absolute and 4.74 relative risk) in bevacizumab-treated metastatic breast cancer [34].

Markedly increased combined end point of *myocardial infarction, HF or cardiovascular death* (11%) in sunitinib-treated imatinib-resistant GIST<7 months of drug beginning with high rate of new hypertension (47%), *EF decline* ≥ 20% (15%), and *troponin* elevation (18%) [32].

Highest *thrombosis rate* (42%) with newest agents such as semaxanib, whose investigation was discouraged [36].

Cardiac adverse outcome (half less likely, 5 vs 9%, in patients with higher basal IGF-1 serum levels) and shorter overall survival in NSCLC receiving adjunctive figitumumab vs standard chemotherapy [37–39], despite inducing a high tumor response rate of 64%.

Observational: *peripheral and coronary atherothrombosis* (30%) with nilotinib [23].

Global cardiovascular complications up to 40% [5] also requiring intensive care admission (10%) [5].

Suggested clinical monitoring, diagnosis and treatment

Clinical assessment: history, a priori IHD risk, GRACE risk score, symptoms, acute BP derangements, basal and on-symptoms ECG (ischemic and QTc variations), proactive ACS detection and monitoring in the period at risk [2], with possible gain of 14,000 € for thrombotic event [86].

Blood determinations: 1 week–1 month troponin [70], BNPs [73], endothelial damage markers (for research purpose), insulin sensitivity [75], GF levels [36].

Instrumental assessment: basal standard echocardiogram [2], with an emphasis on targeting regional a/dyskinesia areas, provocative ischemic testing (myocardial scintigraphy, exercise stress test [75–80]), if needed coronary angiography.

Treatment: aspirin, enoxaparin [76–79], thienopyridines (?), ACE-I, statins, anti-hypertensives [85], if needed coronary percutaneous intervention/CABG/PM/ICD.

2. Pharmacology of angiogenesis inhibitors

Angiogenesis is a known critical determinant of cancer progression, and therefore a major goal of therapeutic drug development. Consequently, angiogenesis inhibitors targeting VEGF have been purposely developed. Nevertheless a first study by Kerbel [6] showed that "accidental" anti-angiogenic properties could be assigned also to so-called conventional antitumoral drugs, by the achievement of

Please cite this article as: Conti E, et al, Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.01.052

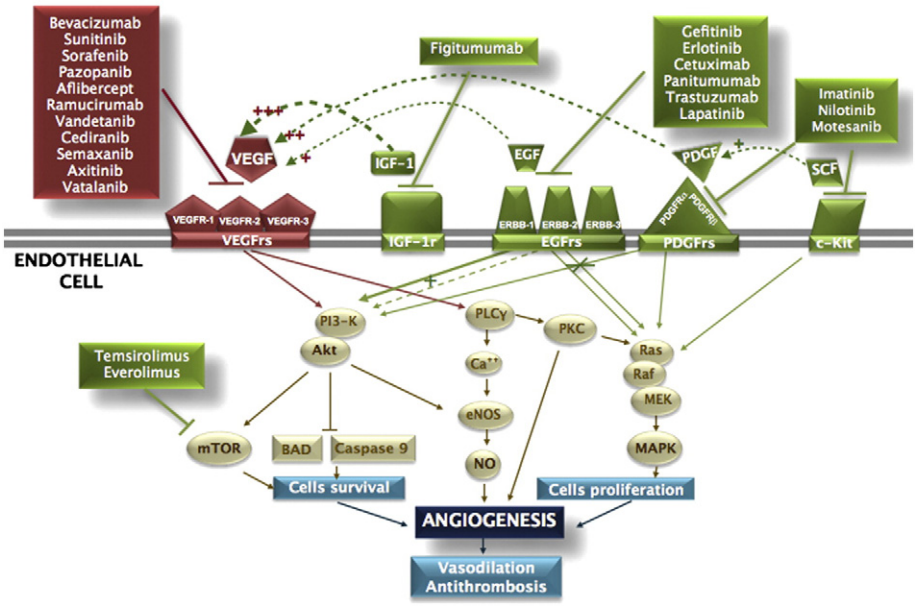

Fig. 1. The "broad" anti-angiogenic network and inhibitors, with redundancies and feedbacks. In red: proper "intended" angiogenic pathways, inhibitors, receptors and ligand. In green broad unintended or "accidental" angiogenic pathways, inhibitors, receptors and ligands. In light yellow intracellular pathways. In blue and light blue final effects on vascular system. EGF: epidermal growth factor; EGFRs: EGF receptors (ERBB-1, ERBB-2, ERBB-3); IGF-1: insulin-like growth factor-1; PDGF: platelet-derived growth factor; PDGFRs: PDGF receptors; SCF: stem cell factor; VEGF: vascular endothelial growth factor; and VEGFRs: VEGF receptors (-1, -2, -3). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Modified with permission from [2].

an indirect inhibition of VEGF synthesis. To this class of "accidentally" antiangiogenic drugs other tyrosine kinase (TK) receptors blockers also appear to belong, subsequently developed and named TK inhibitors (TKI), currently representing a relevant therapeutic option for metastatic or relapsing cancer patients.

In agreement with the seminal paper by Kerbel it appears therefore possible to classify cancer drugs as "proper" intended or "accidental" antiangiogenic therapies, according to their direct or indirect inhibition of VEGF axis. Angiogenic process is indeed realized by a redundant, intricate network, mainly effected by VEGF, but centrally organized by IGF-1 [7], as the critical inducer of VEGF and other growth factors, which all finally converge on serine treonine kinases AKT and mammalian target of rapamycin (mTOR) [2]. The prototypical angiogenic player is VEGF-A, but IGF-1, PDGF, EGF [8], and c-Kit are also involved in a "broad", redundant, VEGF synthetizing and Akt activating network, reciprocally interconnected by positive feedbacks. All growth factors except VEGF, thus, are able to realize an "accidental" unintended angiogenic effect [2], by promoting and enhancing VEGF synthesis or by directly amplifying Akt and mTOR pathways, and finally mediating a stronger endothelial cell survival and proliferation signal [2] (Fig. 1). Drugs targeting this "broad" angiogenic network, consequently realize a "broad" antiangiogenic effect. The ensuing antiangiogenic inherent activity of many of these anticancer drugs has not been purposely investigated in clinical trials (Table 2), and some informations come from observational studies or from in-depth analysis of phase II or randomized trials.

Bevacizumab, which is the prototypical antiangiogenic drug as being an anti-VEGF-A antibody, was firstly approved for metastatic colon cancer in combination with standard chemotherapy, and subsequently for renal cell (RCC), non-small cell lung (NSCLC) and metastatic breast cancers [9]. Subsequently, three more powerful drugs, currently known as plain "anti-antiangiogenic" drugs, multiple TKIs against VEGF receptor-1, -2, -3 (VEGFR-1, -2, -3), as well as against PDGF receptor-α,-β (PDGFR-α,-β) and c-Kit have been approved: sorafenib, for metastatic RCC and unresectable hepatocellular carcinoma (HCC) [4,10], and sunitinib and pazopanib for metastatic RCC [11,12].

Lastly, "targeted" cancer drugs, also including those not directly interfering with VEGF pathway, have rapidly become a widespread therapeutic strategy. Among them, those targeting PDGF, EGF and ERBB-1/ERBB-2-2 are mainly used in colorectal, lung and breast cancers or gastrointestinal stromal tumor (GIST), while mTOR inhibitors temsirolimus and everolimus have been approved for RCC [13,14]. Many available and ongoing studies aim to define the optimal use of both drugs with intended "proper" (Table 1) or unintended "accidental" (Table 2) antiangiogenic effect in different tumor types. The most recent frontier of investigation in this field is represented by the development of new molecules interfering with IGF-1 receptor (IGF-1R) pathway, alone or in combination with chemotherapy or endocrine therapies (Table 2).

As a whole, the entire class of TKI drugs is believed to have a more favorable efficacy/safety profile, as compared with conventional chemotherapy, which indeed counteracts DNA replicating activities of cancer and host cells, frequently achieving severe side effects, especially in tissues at high mitotic index like blood or epithelia. The targeted therapy has profoundly modified the management of many cancers including colorectal, kidney, breast, non-small cell lung cancers, and GIST, as simultaneously achieving improved anti-tumor activity and reduced toxicity compared with traditional chemotherapy [15,16]. First-line gefitinib in lung cancer could be representative of this outcome benefit, achieving a prolonged progression-free survival (PFS) as compared with systemic chemotherapy (HR for progression-free survival 0.43(95% CI 0.32–0.58, <0.001) [17]) or also bevacizumab in colorectal cancer in addition to chemotherapy (median overall survival and progression-free survival (PFS) gains respectively of 5 and 4 months) [18] and sunitinib in renal cancer as compared with interferon alfa (median PFS gain 6 months and higher objective response (31% vs 6%, $p<0.001$)) [19]. The most striking advantage is realized in metastatic GIST treatment, by the TKI imatinib as compared with traditional chemotherapy (response rate 80 vs 10% and median overall survival gain of 39 months [20,21].

Nevertheless, the TKI family, by targeting TKs, involved in a large variety of cellular transductions, concurrently interferes with a large body of enzymatic activities [22] and exhibits a wide series of side

Please cite this article as: Conti E, et al, Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.01.052

Table 1
Contemporary "intended" angiogenesis inhibitors approved for clinical use or in phase III development. CRC: Colorectal Cancer; GIST: Gastrointestinal Stromal Tumors; HCC: Hepatocarcinoma; NSCLC: Non Small Cell Lung Cancer; and RCC: Renal Cell Carcinoma.

Contemporary "intended" anti-angiogenic TKI				
Generic name	Commercial name	Targeted kinase system	Malignancy	State
Bevacizumab	Avastin ®	VEGF-A, VEGFR-1, -2	CRC, NSCLC, glioblastoma multiforme	Approved
Sunitinib	Sutent ®	VEGFR1-2-3, PDGFR α-B, Flt-3, c-Kit, RET, CSF-1R	RCC, GIST	Approved
Sorafenib	Nexavar ®	Raf, VEGFR-2-3, PDGFR-β, c-Kit	RCC, HCC	Approved
Pazopanib	Votrient ®	VEGFR1-2-3, PDGFR-α-β, c-Kit	RCC	Approved
Aflibercept (VEGF Trap)	Zaltrap™	VEGF-A and PlGF	CRC, NSCLC, prostate and pancreatic cancer	Under investigation
Ramucirumab	IMC-1121B	VEGFR2	HCC, breast and gastric adenocarcinoma	Under investigation
Vandetanib	Zactima™	VEGFR-2, EGFR, RET	NSCLC	Under investigation
Cediranib	Recentin™	VEGFR1-2-3, PDGFR-β, c-Kit	NSCLC, CRC	Under investigation
Semaxanib	SU 5416	VEGFR inhibitor	Solid tumors	Under investigation
Axitinib	AG-013736	VEGFR1-2-3, PDGFR, c-Kit	Pancreatic cancer, RCC	Under investigation
Vatalanib	PTK787/ZK222584	VEGFR1-2-3, PDGFR-β, c-Kit	CRC	Under investigation

effects. Atherothrombotic events, the clinical implications of which are being increasingly recognized, represent a relevant portion of these.

3. (Athero) thrombosis and ACS

Accelerated atherogenesis with superimposed thrombosis was dramatically represented, both in cardiac and in peripheral vessels, in a small observational study on administration of nilotinib, an unintended "accidental" angiogenesis inhibitor, not a direct VEGFR inhibitor, which quantified an incidence of acute short-term vascular events up to 30% [23]. This single report is paradigmatic of the relevant doubts possibly arising about the vascular safety of this class of drugs, when it is not proactively inquired, monitored and prevented. Although robust data from prospective randomized studies are lacking, ACS are nonetheless considered a potential side effect of these drugs, on the basis of observational data showing cardiac complications up to 40% [3–5,24–27] and even displaying a 10% rate of serious cardiovascular side effects requiring intermediate or intensive care admission [5].

First data coming from randomized or phase II studies were little impressive in the initial stages of analysis. However these first investigations excluded at risk, multimorbid elderly patients, while later ones considering different cohorts and cancers showed more relevant higher figures of cardiovascular complications. A significant 1.5% rate of ATEs with bevacizumab compared with basal therapy (paclitaxel and carboplatin) has been reported in the first study in advanced NSCLC [28]. A similar incidence of arterial and venous thrombosis has been described in patients with mTOR inhibitors such as everolimus (1.9% cerebral infarction rate [29]) and temsirolimus (2.8% pulmonary embolism rate [30]).

A meta-analysis of trials with the TKIs sorafenib or sunitinib in more than 10,000 patients, showed a similar rate of ATEs (three-fold increased, 2% absolute risk) from these drugs, regardless of the type of malignancy or of TKI [4].

Higher complication rates were conversely reported in sorafenib-treated HCC [9] (5% all grade hypertension rate, 3% myocardial ischemia and infarction rate) and RCC (17% all grade hypertension rate, 4.9% myocardial ischemia or infarction reported rate and 1.5% cerebral ischemia rate [31]) along with sunitinib-treated GIST (4% grade 3/4 hypertension [32]) and RCC (8% grade 3/4 hypertension [33]). Even more relevant results were reported in bevacizumab-treated metastatic breast cancer, with a surprising rate of 15% severe hypertension, 2% cerebrovascular ischemia [34], and 1.6% absolute and 4.74 relative risk of heart failure (HF) [35] compared with placebo-treated patients.

The most striking case among randomized evidence, is that of sunitinib-treated patients with imatinib-resistant GIST, experiencing, within a median time of 7 months, a combined cardiovascular end point as high as 11%, including myocardial infarction, HF or cardiovascular death. In addition relevant and separate event rates were found of new hypertension (47%), ejection fraction decline ≥20% (15%), and troponin elevation (18%) [31]. Most surprisingly, the investigation of newest agents such as semaxanib, was discouraged because of the remarkably higher thrombosis rate of 42% [36].

Lastly, the central knot of the wide angiogenic growth factor network, namely IGF-1, has been targeted. IGF-1R inhibitors have been recently investigated in first line studies and as a useful adjunct to standard therapy against pancreatic cancer and NSCLC, and in trastuzumab- and other drugs-resistant cancers, such as breast, colorectal, prostate, and cervical tumors in which they have achieved durable stable disease [37]. Regretfully, though inducing a high response

Table 2
Contemporary "accidental" angiogenesis inhibitors approved for clinical use or in phase III development. CML: Chronic Myelogenous Leukemia; CRC: Colorectal Cancer; DFSP: Dermatofibrosarcoma protuberans; GIST: Gastrointestinal Stromal Tumors; HNT: Head and Neck Tumors; NSCLC: Non Small Cell Lung Cancer; and RCC: renal cell carcinoma.

Contemporary "accidental" anti-angiogenic TKI				
Generic name	Commercial name	Targeted kinase	Malignancy	State
Imatinib	Glivec®	ABL(bcr-abl), c-Kit, PDGFR	GIST, CML, DFSP	Approved
Nilotinib	Tasigna®	ABL(bcr-abl), c-Kit	CML, GIST	Approved under investigation
Gefitinib	Iressa®	ERBB1	NSCLC	Approved
Erlotinib	Tarceva®	ERBB1	NSCLC	Approved
Cetuximab	Erbitux®	ERBB1	HNT, CRC	Approved
Panitumumab	Vectibix®	ERBB1	CRC	Approved
Trastuzumab	Herceptin®	ERBB2	Breast and gastric cancer	Approved
Lapatinib	Tyverb®	ERBB1, ERBB2	Breast cancer	Approved
Motesanib	AMG-706	cKit, PDGFR	NSCLC, GIST, thyroid and breast cancer	Under investigation
Figitumumab	CP-751,871	IGF-1R	NSCLC, prostate, breast and colon cancers and Ewing's sarcoma.	Under Investigation
Temsirolimus	Torisel®	m-TOR	RCC	Approved
Everolimus	Afinitor®	m-TOR	RCC	Approved

Please cite this article as: Conti E, et al, Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.01.052

rate of 64% [38], data from a large multicenter phase III trial in NSCLC indicate a shorter overall survival in patients receiving adjunctive figitumumab compared with standard chemotherapy, mainly due to cardiac events, dehydration, hyperglycemia, and hemoptysis [39]. Remarkably, the fatal adverse outcomes were half less likely (4.6 vs 8.6%) in patients with higher basal IGF-1 serum levels, compared with those with lower levels [37,38] (Fig. 2).

4. Pathophysiology

Drug-induced endothelial cell damage is the pivotal step by which antiangiogenic drugs may generate the atherothrombotic events underlying ACS [1,2,4]. Cardiovascular adverse outcomes are characterized by their early onset after initiation of therapy, with a median time of event occurrence after drug beginning of 7 months (1 to 12 months), or even much shorter (2.5 months) when administration of erythropoietin stimulating agents was associated [2]. As in spontaneous atherothrombosis models [40,41], fissured endothelial lining and complicated atherosclerotic plaques induced by apoptosis [42,43], may represent the established substrates of these atherothrombotic events. In addition both drug and cancer activities promote damaged endothelium shifting from its anticoagulant properties into procoagulant properties by exposing subendothelial tissue factor and von Willebrand factor [44]. However, concurrent and triggering factors, including cancer-related thrombogenicity, drug-related accelerated atherogenesis and drug-induced hypertension generating high shear-stress at plaque sites [2] are also involved in atherothrombosis associated with the administration of anti-angiogenetic drugs [45]. Proper VEGF inhibitors, TKIs [44] and IGF-1R inhibitors [46] have been proved to be associated with a higher on-treatment platelet reactivity [47], increased endothelial–platelet interactions [48], and thrombosis risk compared with placebo. Furthermore, malignant transformation itself has been associated with higher thrombosis rate, due to an increased production of prothrombotic apoptotic endothelial [49].

Endothelial cell apoptosis is a direct product of both cancer and anti-cancer drugs [42,43], and has been related to atherothrombosis development [50]. It is both a marker of vascular damage and a thrombosis enhancer, by binding tissue factor and by increasing formation [51]. Furthermore, apoptotic endothelial blebs may sustain vascular inflammation, by inducing complement activation [52].

Leukocytosis itself [53], and even cell free DNA produced through cell lysis induced by inflammation and by anticancer drugs, have been shown to promote thrombosis in this class of patients [54]. Besides, autoimmune phenomena, arising in cancer natural history as antiphospholipid antibodies [55], or amplified by drugs as bevacizumab [56], may contribute to atherothrombosis development [57,58].

Moreover antiangiogenic drugs are known to hinder the recognized insulin anti-atherogenic actions, such as glucose uptake [59,60], lipogenesis and antilipolysis [61], ultimately producing a thrombophilic hyperglycemic, atherogenic lipoprotein- and free fatty acid-rich environment, prone to atherothrombosis [1,2]. In particular mTOR inhibitors were almost invariably associated with combined dyslipidemia [29] and hyperglycemia [28,29]. The two latter immune and metabolic damage mechanisms both seem to participate in the peculiar "niche" vasculitis termed cholesterol emboli syndrome, described by some authors as the causal mechanism of vascular damage induced by bevacizumab [62]. Lastly, individual variability in the effectiveness of the described growth factor network, depending on both serum levels or genetic background of IGF-1 or VEGF, accounts for patient susceptibility to the efficacy of anticancer drugs or for different vulnerability to their side effects [1,2,4] (Fig. 3).

5. Management

Although a much deeper and extensive future investigation is deserved, some clues for diagnostics and therapeutics may be derived by data available in patients subjected to proper or accidental antiangiogenic TKI drugs and developing ACS and atherothrombotic coronary heart disease. While frequently overlooked or misdiagnosed, increasingly detected ACS represent a challenge for the common assumption that the cardiotoxicity of anticancer drugs is mainly represented by dilated-hypokinetic cardiomyopathy [63].

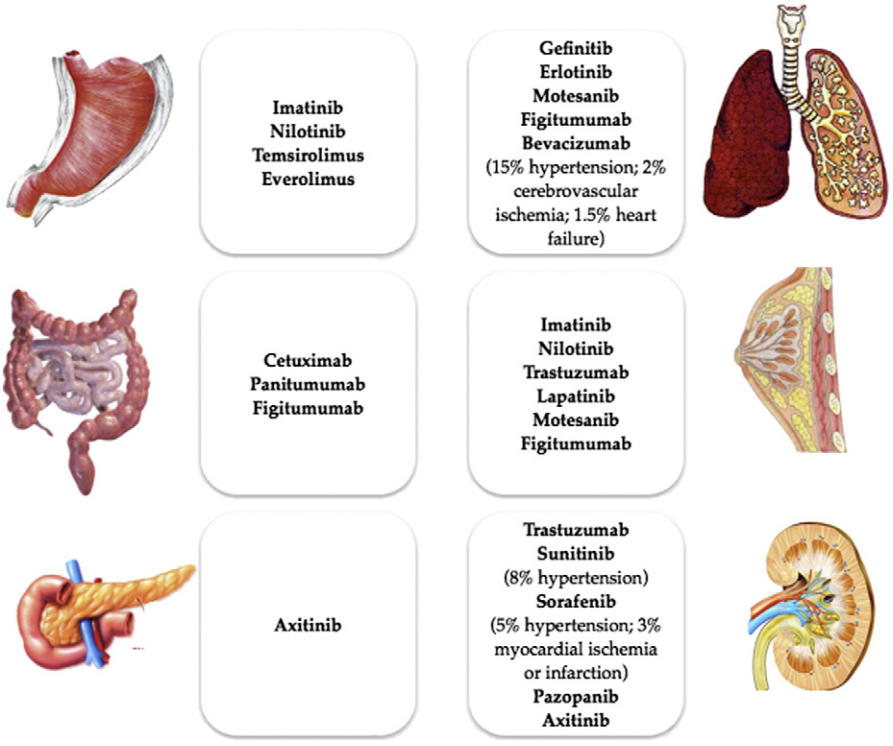

Fig. 2. Most used "accidental" and "proper" antiangiogenic drugs with targeted cancers and organs and relative prevalence of cardiovascular side effects.

Please cite this article as: Conti E, et al, Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.01.052

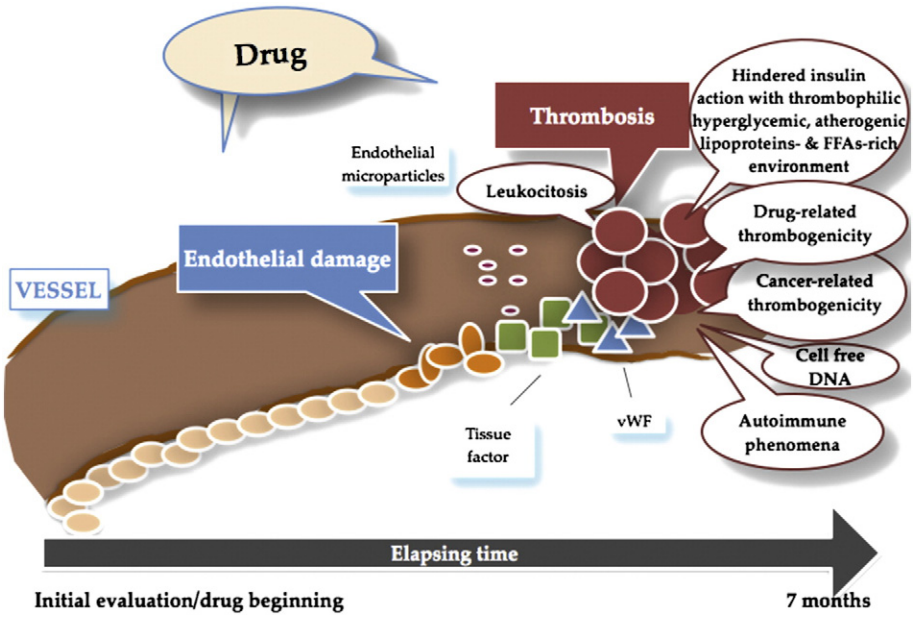

Fig. 3. Proposed pathophysiological mechanisms of vascular atherothrombosis in cancer. Multiple concurring pathways, finally converging on endothelial damage and thrombosis. vWF: von Willebrandt factor.

The first diagnostic step in detecting ACS as a consequence of TKI treatment, therefore crucially relies on the taking into consideration of this often overlooked possibility. Secondly a clinical assessment of the "a priori" cardiovascular ischemic risk of patients subjected to proper or "accidental" antiangiogenic drugs appears useful both to assess the likelihood of coronary heart disease and the appropriate prognosis. Indeed, patients more than 65 years of age, with diabetes or a previous cardiovascular event, especially in the absence of aspirin prescription [64], and in the presence of a higher Framingham risk score [65], were suggested to possibly identify susceptibility to atherothrombotic effect of bevacizumab [2]. Nevertheless, large studies verifying the predictive role of this as well as of other models such as GRACE [66], with reference to the evaluation of patients who are "vulnerable" to the atherothrombotic effects of TKI, are lacking. It would be particularly valuable to verify whether GRACE risk score, featured by a better performance in secondary prevention after ACS, incorporating renal function assessment, and performing as high as troponin values [67] would acceptably fulfill the task of predicting atherothrombotic events in cancer patients undergoing "targeted" therapies. Troponin values have been indeed shown to early detect a high proportion of patients with TKI-induced cardiac involvement and to rule out cardiac complication with a higher than 70% rate [68]. Troponin assay, as well, has been acknowledged by expert panels as the ideal cardiac marker for the identification and monitoring of drug-induced cardiac injury, for its high specificity, sensitivity, wide diagnostic window (up to 15 days) and robustness [69]. Moreover, in the past, the robust and long-term negative predictive value of basal and early (first week and first month) troponin for later development of adverse cardiac event after traditional chemotherapy [70] was consolidated.

As a result, by allowing a close and effective cardiological monitoring, troponin evaluation has been suggested to be included at the starting point of a decisional tree designed to evaluate cardiovascular side effects of cancer drugs. Nevertheless, a correct differential interpretation of the different causes of troponin elevation, ranging from coronary atherothrombosis, of which this necrosis marker can be a proxy [71,72], to acute cardiomyopathy/left ventricular (LV) dysfunction, pulmonary embolism and myocarditis/pericarditis, plainly requires cardiological expert consultation.

Other studied markers include natriuretic peptides such as brain natriuretic petide (BNP) and its fragment NTproBNP, which increase with the development of HF after cancer treatment [73] and were suggested as possible early predictors of long term cardiac outcome [74]. Interesting final monitoring markers, possibly of major interest for research than for diagnostic clinical purpose, are the markers of endothelial dysfunction such as serum intercellular cell adhesion molecule (sICAM) or circulating endothelial cells, which were still found to be later increased in long term survivors of cancer after chemotherapy, contrary to chemotherapy-naïve survivors. These markers were associated with clinical features of insulin resistance and metabolic syndrome [75], of which it is interesting to remind the link with both cardiovascular disease and outcome, as well as with reduced IGF-1 and VEGF serum levels [1,2,36]. However, despite being clearly associated with cancer therapy and being a proxy of cardiovascular events, these markers of endothelial dysfunction were never investigated as prognosticators of long term cardiovascular outcome in cancer populations.

Beyond collecting history, cardiovascular risk profile and scores and measuring monitoring markers, pertinent indications should be formulated for cardiac diagnostic strategies such as a proactive detection of ACS in the "at risk" period, including symptoms, electrocardiogram (ECG) and troponin joint evaluation [2], or inducible ischemia detection by exercise stress test or myocardial scintigraphic imaging [2,76,77]. Nuclear imaging detection of myocardial ischemia or dysfunction, though rarely employed [78], similarly confirmed early cardiac ischemia onset within 6–12 months of chemotherapy and radiotherapy in over 40% of a series of breast cancer patients [79]. An even more basic diagnostic tool such as echocardiography gathered evidence against a reversibility of cardiotoxicity of trastuzumab used in breast and bowel cancer [80]. Second level diagnostics such as coronary angiography should be scheduled as required by clinical assessment.

As to the recommended therapy to be instituted for the atherothrombosis risk in cancer patients undergoing proper or "accidental" antiangiogenic drugs, preventive antiplatelet or anticoagulant therapy is coherently advisable due to the known thrombosis risk of TKI-treated cancer patients. As expected, aspirin therapy has been shown to be associated with a significant improved short-term global outcome [81], and, surprisingly, even in small cohorts of thrombocytopenic patients [82]. Even though there are few randomized studies

Please cite this article as: Conti E, et al, Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.01.052

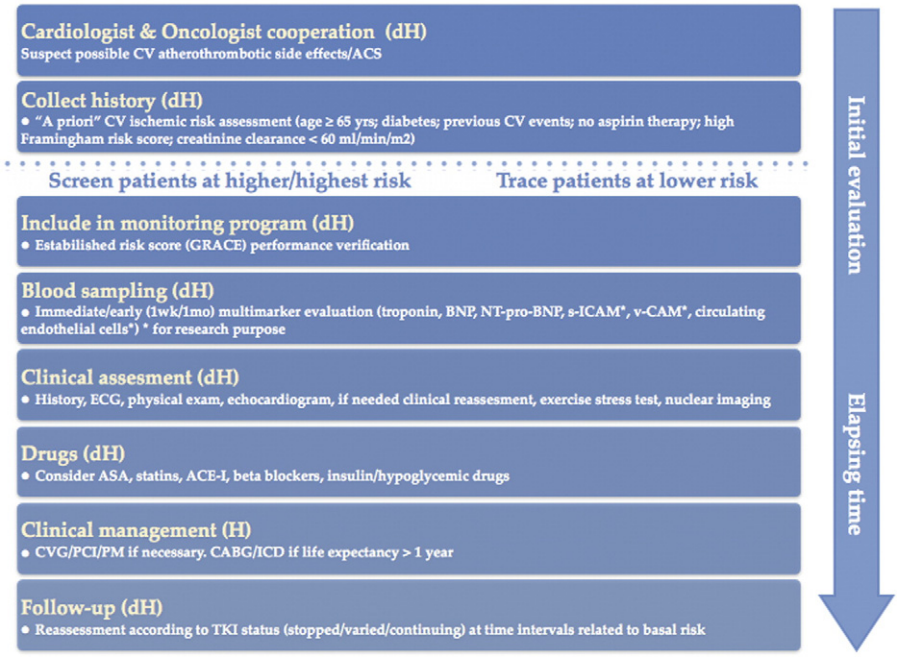

Fig. 4. Proposed flowchart of cardiovascular assessment in patients undergoing TKI therapy. ACE-I: angiotensin converting enzyme inhibitors; ACS: acute coronary syndromes; ASA: aspirin; BNP: brain natriuretic peptide, CABG: coronary artery bypass graft; CV: cardiovascular; CVG: coronary ventricular angiography; ECG: electrocardiogram; ICD: implantable cardiac defibrillator; NT-proBNP: NT-pro-brain natriuretic peptide; PCI: percutaneous coronary intervention; PM: pace-maker; s-ICAM: soluble intercellular cell adhesion molecule; v-CAM: vascular cell adhesion molecule-1; TKI: tyrosine kinase inhibitors; dH: day hospital evaluation; and H: hospital evaluation.

in solid cancer, data coming from hematologic malignancies advise preferred low-dose low-molecular weight heparin rather than warfarin, and low [83] to medium [84] dose aspirin. Furthermore, an appropriate hemorrhagic risk stratification, according to one of the several known bleeding risk scores, could be useful [2]. Comparable gains in overall survival were proven with antihypertensive drugs [85].

Similarly, antioxidant and endothelial protective properties of statins and ACE-inhibitors are theoretically relevant and functional to dampen the anti-angiogenic drugs derived atherothrombotic risk [1,2]. In the case of ACS or of documented inducible myocardial ischemia, a pertinent therapeutic management could include coronary angiography or percutaneous intervention, and even coronary artery bypass graft or cardiac pace maker or implantable defibrillator.

The use of such preventive, early diagnostic, and therapeutic strategies is expected to improve the length and cost of hospitalization for atherothrombotic toxicities of these so-called "targeted" cancer drugs. Indeed estimated expenses from cardiac hospitalizations due to the ensuing cardiotoxicity of these drugs, are reported to be as relevant as 14,000 € per atherothrombotic event, even requiring up to 15 (±21) day-long hospitalizations [86].

Finally, in their follow-up, treated patients who present the possible ensuing ATEs, could relapse and consequently could need to be further evaluated for a second-line treatment with traditional chemotherapy or with both on- and off- [87] label use of different TKIs. In the latter cases their cardiological follow-up should continue and the therapeutic strategy should be re-assessed with a specific attention to the stratification for atherothrombotic cardiovascular risk, with a continuous, surveillance and hospitalizations as needed for recurrent atherothrombotic events (Fig. 4).

References

[1] Conti E, Musumeci MB, De Giusti M, et al. IGF-1 and atherothrombosis: relevance to pathophysiology and therapy. Clin Sci 2011;120:377–402.
[2] Passerini J, Romiti A, D'Antonio C, et al. Tailored angiogenesis inhibition in cancer therapy: respecting the heart to improve the net outcome. Curr Signal Transduct Ther 2012;24:265–88.
[3] Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–34.
[4] Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. J Clin Oncol 2010;28:2280–5.
[5] Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2008;26:5204–12.
[6] Kerbel RS, Viloria-Petit A, Klement G, Rak J. "Accidental" anti-angiogenic drugs: anti-oncogene directed signal transduction inhibitors and conventional chemotherapeutic agents as examples. Eur J Cancer 2000;36:1248–57.
[7] Slomiany MG, Rosenzweig SA. Hypoxia-inducible factor-1-dependent and -independent regulation of insulin-like growth factor-1-stimulated vascular endothelial growth factor secretion. J Pharmacol Exp Ther 2006;318:666–75.
[8] Pasquier E, Kavallaris M, André N. Metronomic chemotherapy: new rationale for new directions. Nat Rev Clin Oncol 2010;7:455–65.
[9] Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004;3:391–400.
[10] Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma (HCC). N Engl J Med 2008;359:378–90.
[11] Goodman VL, Rock EP, Dagher R, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. Clin Cancer Res 2007;13:1367–73.
[12] Keisner SV, Shah SR. Pazopanib in the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma. Drugs 2011;71:443–54.
[13] Kwitkowski VE, Prowell TM, Ibrahim A, et al. FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma. Oncologist 2010;15:428–35.
[14] Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449–56.
[15] Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med 2005;353:172–87.
[16] Imai K, Takaoka A. Comparing antibody and small-molecule therapies for cancer. Nat Rev Cancer 2006;6:714–27.
[17] Wang F, Wang LD, Li B, Sheng ZX. Gefitinib compared with systemic chemotherapy as first-line treatment for chemotherapy-naive patients with advanced non-small cell lung cancer: a meta-analysis of randomised controlled trials. Clin Oncol (R Coll Radiol) 2012;24:396–401.
[18] Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.
[19] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
[20] Dematteo R, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumours: before and after STI-571. Hum Pathol 2002;33:466–77.

Please cite this article as: Conti E, et al, Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.01.052

[21] Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620–5.
[22] Chen MH, Kerkela R, Force T. Mechanism of cardiomyopathy associated with tyrosine kinase inhibitor cancer therapeutics. Circulation 2008;118:84–95.
[23] Aichberger KJ, Herndlhofer S, Schernthaner GH, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. Am J Hematol 2011;86:533–9.
[24] Ederhy S, Massard C, Dufaitre G, et al. Frequency and management of troponin I elevation in patients treated with molecular targeted therapies in phase I trials. Invest New Drugs 2010, doi:10.1007/s10637-010-9546-8.
[25] Daher IN, Yeh ET. Vascular complications of selected cancer therapies. Nat Clin Pract Cardiovasc Med 2008;5:797–805.
[26] Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011–9.
[27] Kerkelä R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med 2006;12:908–16.
[28] Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.
[29] Doi T, Muro K, Boku N, et al. Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer. J Clin Oncol 2010;28:1904–10.
[30] Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. Br J Cancer 2006;95:1148–54.
[31] Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27:3312–8.
[32] Rock EP, Goodman V, Jiang JX, et al. Food and Drug Administration drug approval summary: sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma. Oncologist 2007;12:107–13.
[33] Adams VR, Leggas M. Sunitinib malate for the treatment of metastatic cell carcinoma and gastrointestinal stromal tumors. Clin Ther 2007;29:1338–53.
[34] Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666–76.
[35] Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomized, double-blind phase III trial. Lancet 2007;370:2103–11.
[36] Kuenen BC, Rosen L, Smit EF, et al. Dose finding and pharmacokinetic study of cisplatin, gemcitabine, and SU5416 in patients with solid tumors. J Clin Oncol 2002;20:1657–67.
[37] Gualberto A, Pollak M. Emerging role of insulin-like growth factor receptor inhibitors in oncology: early clinical trial results and future directions. Oncogene 2009;28:3009–21.
[38] Karp DD, Paz-Ares LG, Novello S, et al. Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2009;27:2516–22.
[39] Jassem J, Langer CJ, Karp DD, et al. Randomized, open label, phase III trial of figitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin in patients with non-small cell lung cancer. Best of ASCO San Francisco. Abstract 2010, 28;7500 Presented July 17; 2010.
[40] Fernandez-Hernando C, Ackah E, Yu J, et al. Loss of Akt1leads to severe atherosclerosis and occlusive coronary artery disease. Cell Metab 2007;6:446–57.
[41] Fernandez-Hernando C, Jozsef L, Jenkins D, Di Lorenzo A, Sessa WC. Absence of Akt1 reduces vascular smooth muscle cell migration and survival and induces features of plaque vulnerability and cardiac dysfunction during atherosclerosis. Arterioscler Thromb Vasc Biol 2009;29:2033–40.
[42] Rak J. Microparticles in cancer. Semin Thromb Hemost 2010;36:888–906.
[43] Mostefai HA, Andriantsitohaina R, Martínez MC. Plasma membrane microparticles in angiogenesis: role in ischemic diseases and in cancer. Physiol Res 2008;57:311–20.
[44] Elice F, Rodeghiero F, Falanga A, Rickles FR. Thrombosis associated with angiogenesis inhibitors. Best Pract Res Clin Haematol 2009;22:115–28.
[45] Winn R, Harlan J. The role of endothelial cell apoptosis in inflammatory and immune diseases. J Thromb Haemost 2005;3:1815–24.
[46] Olmos D, Postel-Vinay S, Molife LR, et al. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. Lancet Oncol 2010;11:129–35.
[47] Lynch DR, Kickler TS, Rade JJ. Recurrent myocardial infarction associated with gefitinib therapy. J Thromb Thrombolysis 2011;32:120–4.
[48] Verheul HMW, Pinedo HM. Possible molecular mechanism involved in the toxicity of angiogenesis inhibition. Nat Rev Cancer 2007;7:475–85.
[49] Lima LG, Oliveira AS, Campos LC, et al. Malignant transformation in melanocytes is associated with increased production of procoagulant microvesicles. Thromb Haemost 2011;106:712–23.
[50] Morel O, Pereira B, Averous G, et al. Increased levels of procoagulant tissue factor-bearing microparticles within the occluded coronary artery of patients with ST-segment elevation myocardial infarction: role of endothelial damage and leukocyte activation. Atherosclerosis 2009;204:636–41.
[51] Bombeli T, Karsan A, Tait JF, Harlan JM. Apoptotic vascular endothelial cells become procoagulant. Blood 1997;89:2429–42.
[52] Mold C, Morris CA. Complement activation by apoptotic endothelial cells following hypoxia/reoxygenation. Immunology 2001;102:359–64.
[53] Connolly GC, Khorana AA, Kuderer NM, Culakova E, Francis CW, Lyman GH. Leukocytosis, thrombosis and early mortality in cancer patients initiating chemotherapy. Thromb Res 2010;126:113–8.
[54] Swystun LL, Mukherjee S, Liaw PC. Breast cancer chemotherapy induces the release of cell-free DNA, a novel procoagulant stimulus. J Thromb Haemost 2011;9:2313–21.
[55] Sanon S, Lenihan DJ, Mouhayar E. Peripheral arterial ischemic events in cancer patients. Vasc Med 2011;16:119–30.
[56] Vihinen P, Paija O, Kivisaari A, Koulu L, Aho H. Cutaneous lupus erythematosus after treatment with paclitaxel and bevacizumab for metastatic breast cancer: a case report. J Med Case Reports 2011;5:243.
[57] Matsuura E, Lopez LR. Autoimmune-mediated atherothrombosis. Lupus 2008;17:878–87.
[58] Cederholm A, Frostegård J. Annexin A5 as a novel player in prevention of atherothrombosis in SLE and in the general population. Ann N Y Acad Sci 2007;1108:96–103.
[59] Hong DS, Sebti SM, Newman RA, et al. Phase I trial of a combination of the multikinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in advanced malignancies. Clin Cancer Res 2009;15:7061–8.
[60] Haluska P, Worden F, Olmos D, et al. Safety, tolerability, and pharmacokinetics of the anti-IGF-1R monoclonal antibody figitumumab in patients with refractory adrenocortical carcinoma. Cancer Chemother Pharmacol 2010;65:765–73.
[61] Schechter Y, Yaish P, Chorev M, Gilon C, Braun S, Levitzki A. Inhibition of insulin-dependent lipogenesis and anti-lipolysis by protein tyrosine kinase inhibitors. EMBO J 1989;8:1671–6.
[62] Mir O, Mouthon L, Alexandre J, et al. Bevacizumab-induced cardiovascular events: a consequence of cholesterol emboli syndrome? J Natl Cancer Inst 2007;99:85–6.
[63] Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy. Clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213–20.
[64] Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007;99:1232–9.
[65] Tebbutt NC, Murphy F, Zannino D, et al. Risk of arterial thromboembolic events in patients with advanced colorectal cancer receiving bevacizumab. Ann Oncol 2011;22:1834–8.
[66] Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndromes. Estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291:2727–33.
[67] Meune C, Drexler B, Haaf P, et al. The GRACE score's performance in predicting in-hospital and 1-year outcome in the era of high-sensitivity cardiac troponin assays and B-type natriuretic peptide. Heart 2011;97:1479–83.
[68] Morris PG, Chen C, Steingart R, et al. Troponin I and C-reactive protein are commonly detected in patients with breast cancer treated with dose-dense chemotherapy incorporating trastuzumab and lapatinib. Clin Cancer Res 2011;17:3490–9.
[69] Expert Working Group on Biomarkers of Drug-Induced Cardiac Toxicity report to the Nonclinical Studies Subcommittee of the Advisory Committee for Pharmaceutical Science. http://www.fda.gov/ohrms/dockets/ac/02/briefing/3891B101Troponin; 2002. [Outline.pdf NICE website press release].
[70] Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004;109:2749–54.
[71] Heeschen C, van Den Brand MJ, Hamm CW, Simoons ML. Angiographic findings in patients with refractory unstable angina according to troponin T status. Circulation 1999;100:1509–14.
[72] Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. Lancet 1999;354:1757–62.
[73] Papazisis KT, Kontovinis LF, Papandreou CN, et al. Brain natriuretic peptide precursor (NT-pro-BNP) levels predict for clinical benefit to sunitinib treatment in patients with metastatic renal cell carcinoma. BMC Cancer 2010;10:489.
[74] Sandri MT, Salvatici M, Cardinale D, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotherapy: a marker predictive of cardiac dysfunction? Clin Chem 2005;51:1405–10.
[75] Vaughn DJ, Palmer SC, Carver JR, Lacobs LA, Mohler ER. Cardiovascular risk in long-term survivors of testicular cancer. Cancer 2008;112:1949–53.
[76] de Geus-Oei LF, Mavinkurve-Groothuis AM, Bellersen L, et al. Scintigraphic techniques for early detection of cancer treatment-induced cardiotoxicity. J Nucl Med 2011;52:560–71.
[77] Tzonevska A, Tzvetkov K, Atanasova M, Chakarova A, Piperkova E. Myocardial scintigraphy, echocardiography and proBNP for early detection of myocardial cardiotoxicity in breast cancer patients after chemo-radiotherapy. Hell J Nucl Med 2011;14:269–73.
[78] Verma S, Ewer MS. Is cardiotoxicity being adequately assessed in current trials of cytotoxic and targeted agents in breast cancer? Ann Oncol 2011;22:1011–8.
[79] Sawaya H, Sebag IA, Plana JC, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol 2011;107:1375–80.
[80] Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol 2007;25:3525–33.
[81] Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thrombo-embolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007;99:1232–9.

Please cite this article as: Conti E, et al, Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.01.052

[82] Sarkiss MG, Yusuf SW, Warneke CL, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. Cancer 2007;109:621–7.
[83] Cavo M, Zamagni E, Tosi P, et al. First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. Haematologica 2004;89:826–31.
[84] Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. Mayo Clin Proc 2005;80:1568–74.
[85] Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 2011;103:763–73.
[86] Overbeek JA, Zhao Z, van Herk-Sukel MP, Barber BL, Gao S, Herings RM. Costs of hospital events in patients with metastatic colorectal cancer. J Med Econ 2011;14:656–61.
[87] Cheng A, Kang Y, Lin D, et al. Phase III trial of sunitinib (Su) versus sorafenib (So) in advanced hepatocellular carcinoma (HCC). J Clin Oncol 2011;29 [Suppl.: abstr 4000].

Please cite this article as: Conti E, et al, Arterial thrombotic events and acute coronary syndromes with cancer drugs: Are growth factors the missed link? Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.01.052