International Journal of Cardiology 167 (2013) 2421–2429

Contents lists available at 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

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ARTICLE INFO

Article history:
Received 15 November 2012
Accepted 18 January 2013
Available online 12 February 2013

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.

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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