Cardiac side effects of molecular targeted therapies: Towards a better dialogue between oncologists and cardiologists

Stephane Ederhy\textsuperscript{a}, Hassan Izzedine\textsuperscript{b}, Christophe Massard\textsuperscript{c}, Ghislaine Dufaitre\textsuperscript{a}, Jean Philippe Spano\textsuperscript{b}, Gerard Milano\textsuperscript{d}, Catherine Meuleman\textsuperscript{a}, Benjamin Besse\textsuperscript{c}, Franck Boccara\textsuperscript{a}, David Kahyat\textsuperscript{b}, Ariel Cohen\textsuperscript{a}, Jean Charles Soria\textsuperscript{c,\ast}

\textsuperscript{a} Saint-Antoine Hospital and University Pierre et Marie Curie VI, Paris, France
\textsuperscript{b} Pitie-Salpetriere Hospital, University Paris et Marie Curie VI, Paris, France
\textsuperscript{c} Institut Gustave Roussy, SITEP, Villejuif and University Paris XI, France
\textsuperscript{d} Centre Antoine Lacassagne, Nice, France

Accepted 18 January 2011

Abstract

Molecular targeted therapies (MTTs) have become a major component of modern management of various hematological and solid malignancies. However, some MTTs have been associated with cardiotoxicity. MTT-induced cardiovascular side effects include left ventricular systolic dysfunction, heart failure, conduction abnormalities, acute coronary syndrome, and hypertension. One of the most threatening complications of MTT, and notably of angiogenic inhibitors, is QT prolongation with the risk of torsades de pointe and sudden death. The precise incidence of cardiovascular events associated with MTT as well as their reversibility are unknown. Here, we summarize what is known about the cardiotoxicity of MTT, emphasizing MTTs that target tyrosine kinases. We have tried to provide both the basic mechanisms underlying

\textsuperscript{\ast} Corresponding author at: Department of Medical Oncology, Institut Gustave Roussy, SITEP, Villejuif, 39 Rue Camille Desmoulins, 94805 Villejuif, France. Tel.: +33 142 11 43 39; fax: +33 142 11 52 17.
E-mail address: soria@igr.fr (J.C. Soria).

1040-8428/$ – see front matter © 2011 Published by Elsevier Ireland Ltd.
doi:10.1016/j.critrevonc.2011.01.009

specific cardiotoxicities (such as the interruption of specific signaling pathways leading to cardiomyocyte dysfunction and/or death), and offer guidance regarding the optimal way to detect and treat these cardiotoxicities.

© 2011 Published by Elsevier Ireland Ltd.

Keywords: Cardiotoxicity; Heart failure; Hypertension; Molecular targeted agent

1. Introduction

Over the last two decades, considerable progress has been achieved in the management of cancer with the introduction and use of molecular targeted therapies (MTTs). MTTs have proven particularly efficient in the treatment of metastatic kidney, breast, colon, lung carcinoma, gastrointestinal stromal tumors (GISTs), and chronic myeloid leukemia [1]. Nevertheless, MTTs can inhibit major pathways in normal or noncancerous cells leading to unexpected off-target side effects, morbidity, reduced drug doses, or even drug cessation [2]. Cardiac toxicities associated with MTT include left ventricular systolic dysfunction (LVSD), heart failure, conduction abnormalities, QT prolongation, acute coronary syndrome, and hypertension [2–10]. Fig. 1 presents an overview of the different cardiotoxicities associated with MTTs. The frequency of MTT-induced cardiotoxicity is largely unknown or potentially underestimated, but would appear to be variable and dependent on the agent used. One of the most threatening complications of MTT is QT prolongation with the risk of torsades de pointe and sudden death [9,10]. MTT-induced cardiotoxicity was first reported with trastuzumab [11–13]. Cases of heart failure have also been reported after treatment with imatinib [5] and adverse cardiac effects are mentioned in the prescribing information for dasatinib, sunitinib, sorafenib, and bevacizumab. Cardiotoxicity should be determined for each agent on a case-by-case basis. Here, we will examine the incidence and molecular mechanisms of MTT-related cardiovascular events.

1.1. Hypertension

1.1.1. Diagnosis and incidence

The treatment of cancer patients with angiogenesis inhibitors, either antibodies or tyrosine kinase inhibitors (TKIs) that target vascular endothelial growth factor (VEGF), is associated with hypertension that can be life-threatening and cause damage to the eyes, brain, or kidneys [14]. When VEGF is blocked by bevacizumab, as high as 20–30% of patients experience BP increases (primarily systolic), 11–16% require de novo antihypertensive treatment, and 1% experience hypertensive crisis [14,15]. When anti-angiogenic TKIs are administered, 15–60% of patients develop hypertension [15]. In a retrospective study of 75 patients treated with sunitinib, Chu et al. [4] found that 47% of patients developed hypertension defined as BP > 150/100 mm Hg. In a study by Veronese et al. [16] 16% of the patients treated with sorafenib experienced increased systolic BP > 20 mmHg. Another side effect that may be related to hypertension is encephalopathy [17]. Several case reports of MTT-associated reversible posterior leukoencephalopathy syndrome (RPLS) have been published [18–20]. The most frequent cause of RPLS is thought to be hypertension, and this might be related to endothelial dysfunction [14].

1.1.2. Mechanisms of hypertension

BP is regulated by cardiac output and blood volume regulation through baroreceptors in the kidneys and the vasculature itself [14]. In in vivo experimental models, VEGF infusion leads to a clear decrease in BP [21,22]. In a clinical trial in which VEGF was used to treat ischemia, a drop of 22% was observed in systolic BP [23]. An inappropriate reduction in capillary and arteriolar density may induce peripheral vascular resistance, resulting in hypertension [24]. Mourad et al. [25] demonstrated that hypertension induced by bevacizumab was associated with capillary rarefaction measured by capillaroscopy, suggesting that the modification of the microcirculation initiates or contributes to an increase in BP [14]. Veronese et al. [16] found that hypertension induced by sorafenib is primarily related to an increase in vascular stiffness, whereas no relationship with humoral factors involved in BP regulation (e.g. catecholamines, aldosterone) or volume expansion was detected.

1.1.3. Management of hypertension

There are no specific recommendations for drug treatment of hypertension secondary to anti-angiogenic therapy nor is there a consensus about what would be the best BP measurement method to detect such a complication. It is important not to withdraw treatment early, but rather to implement active anti-hypertensive therapy with the objective of obtaining BP < 140/90 mmHg. Discontinuation of anti-angiogenic treatment may be applicable if systolic BP is > 200 mmHg or diastolic BP > 100 mmHg or in case of a hypertensive crisis. Antihypertensive therapy in patients with cardiovascular events includes the use of angiotensin-converting enzyme inhibitors and beta-blockers. This approach is consistent with the American Heart Association/American College of Cardiology guidelines for the treatment of heart failure or of patients at high risk of heart failure [26]. Medications that interfere with cytochrome P450 and inhibitors of CYP3A4 (e.g. diltiazem, verapamil) should be avoided as far as possible [27], as many oral anti-angiogenic agents are also cytochrome substrates. Hypertension is a clearly defined risk factor for heart failure and other cardiovascular events and should therefore be treated in cancer patients as in noncancer patients according to national recommendations.
1.2. Left ventricular systolic dysfunction and heart failure

1.2.1. Diagnosis and incidence

The diagnosis of heart failure based on clinical and physical examination remains difficult in daily clinical practice[29]. A high degree of disagreement is found among studies evaluating the diagnostic accuracy of clinical and physical examinations[30]. The sensitivity and specificity of clinical signs do not exceed 75% [31]. No clinical or physical examination is able to discriminate between heart failure with and without LVSD[32].

In cancer patients, dyspnea may be due to different etiologies such as pulmonary embolism, cardiac tamponade, heart failure, or disease progression. In 37 cancer patients receiving chemotherapy, Fromme et al.[33] found that physicians failed to identify one-half of the symptoms patients were experiencing, particularly dyspnea which went undetected in 77% of cases. Moreover, the diagnosis of heart failure is based on the presence of dyspnea, fatigue, and peripheral edema, which are classified as respiratory, constitutional, and lymphatic/cardiovascular symptoms, thus making the diagnosis of congestive heart failure difficult. In this context, the importance of an ‘objective’ biological marker and a prompt echocardiography is crucial in supplementing the clinician’s skills. The tools available are B-type natriuretic peptide (BNP) measurement and echocardiography.

BNP, a neurohormone synthesized by myocytes, is secreted in response to increased myocyte stretching caused by either increased filling or pressure overload[34]. BNP has an excellent negative predictive value for excluding heart failure, particularly when plasma BNP concentration is <100 pg/mL [34]. By contrast, a high level of BNP is not always a marker of heart failure in cancer patients [35].

Echocardiography, which is a noninvasive real-time imaging technique, can be performed at the bedside and easily repeated when needed. According to ACC/AHA guidelines for the diagnosis and management of heart failure, echocardiography is considered the single most useful diagnostic test in the evaluation of patients with heart failure [26].

Trastuzumab. Trastuzumab induces symptomatic or asymptomatic LVSD in 4–7% of patients when it is administered alone and in 27% of patients when it is combined with anthracyclines[36]. Furthermore, significant toxicity was reported (5–17% for asymptomatic LVSD and 1–3% for symptomatic heart failure) in patients treated with chemotherapy and trastuzumab for breast cancer. Risk factors for cardiac toxicity included an advanced age, co-administration of anthracyclines, and previous LVSD. It is important to note that LSVD was generally totally reversible after discontinuation of trastuzumab [37].

ABL inhibitors: imatinib, dasatinib. Retrospective analyses indicate that heart failure in response to imatinib is rare, with a reported incidence of <1% [38,39]. In the randomized
BP measurement at baseline

- Normal BP: < 120/80 mmHg

- Pre-HT: 120-140/80-90 mmHg

- Stage 1 HT: 140-160/90-100 mmHg

- Stage 2 HT: > 160/100 mmHg

Cardiovascular risk factor

- No

- Yes

Start AI therapy

BP monitoring

Start CCB followed when needed by other antihypertensive agents 3-7 days before starting AI therapy

BP monitoring during AI therapy

- every week for first 8 weeks

- and before each infusion or cycle

BP

- < 130/80 mmHg: Continue AI therapy

- ≥ 140/90 mmHg: Hypertensive crisis

Stop AI therapy

Reinforce anti-HT drugs

Reinforce anti-HT drugs

Continue AI therapy

Fig. 2. Management of hypertension induced by angiogenic inhibitors. Abbreviations: AI, angiogenesis inhibitor; CCB, calcium channel blocker; HT, hypertension.

EORTC-ISH-AGITC phase III trial of imatinib, Verweij et al. [39] found an incidence of 0.2% for episodes of heart failure. Imatinib leads to cell death in cultured cardiomyocytes, with features of both apoptosis and necrosis [3]. The pathway mediating cell death appears to be an induced endoplasmic reticulum (ER) stress response [40], in which a buildup of misfolded proteins in the ER induces cellular apoptosis [41]. Imatinib also induces ER stress in chronic myelogenous leukemia (CML) and GIST cells, and this is believed to play a role in inducing their death [42]. The c-Jun N-terminal kinase (JNK) family of stress-activated mitogen-activated protein kinases functions as a key downstream pathway activated by the ER stress response that ultimately mediates cell death [42]. Of note, imatinib-induced cell death was prevented by salubrinal, a compound that protects cells from ER stress and inhibition of JNK [41].

Dasatinib has also been implicated in the development of heart failure with as many as 4% of patients in some series developing congestive heart failure [43]. Although this appears to be due to inhibition of Abl [44] dasatinib also inhibits Src and was recently reported to inhibit a number of other kinases [45].

Lapatinib. Perez and colleagues [46] prospectively analysed cardiac function in 3558 patients treated with lapatinib in 18 phase I–III trials. Lapatinib infrequently affected left ventricular ejection fraction (LVEF), with only 1.6% of patients experiencing a decrease in LVEF. The mean LVEF decrease was 18.7% (range, 11–32%) and mostly asymptomatic (1.4% asymptomatic and 0.2% symptomatic). Among patients pre-treated with anthracyclines, 1.2% experienced a decrease in LVEF, which was symptomatic in 0.3%. Among patients pre-treated with trastuzumab and chemotherapy, 1.7% expe-
rienced a decrease in LVEF, which was symptomatic in only 0.1%. Finally, in 2201 anthracycline- and trastuzumab-naive patients, 1.7% experienced a decrease in LVEF, which was asymptomatic in 0.2% [46]. Thus far, it appears that the effect of lapatinib on the myocardium may be similar to the myocardial effect of trastuzumab. This noncumulative, nondose-related cardiotoxicity is largely reversible and ultrastructural myocardial changes are not generally seen [47,48].

**Multi-kinase inhibitor: sunitinib.** Concerns about the cardiac safety of sunitinib emerged from early clinical trials of the drug. No change in mean LVEF was reported in a trial of patients with advanced GIST after a median treatment duration of 8 weeks [49]. In patients with metastatic renal cell carcinoma, 10% of patients treated with sunitinib experienced LVSD without clinical sequela compared with 3% of those treated with interferon [50]. Another study reported that 4.6% of patients treated with sunitinib developed LVSD defined as a reduction in LVEF > 20% [51].

In a retrospective study on 75 patients treated with sunitinib, Chu et al. [4] showed that 20% of patients exhibited LVEF < 50%, 8% experienced one episode of symptomatic heart failure (class III or IV), and 19% had an LVEF decrease ≥ 15% during monitoring. Schmidinger et al. [8] reported a high frequency of cardiovascular events in patients receiving sunitinib for metastatic renal cell cancer. Among 25 patients receiving sunitinib, six experienced LVEF dysfunction. All patients recovered after cardiovascular management (i.e., medication, coronary angiography, pacemaker implantation, and heart surgery) and were considered eligible for continuation of sunitinib. Statistically, there was no significant difference in survival between patients who experienced a cardiac event and those who did not [8]. In another retrospective analysis, Khakoo et al. [6] found that 6 of 224 (2.7%) patients who received sunitinib developed heart failure which resulted in substantial morbidity and, in some cases, mortality.

Sunitinib induces the inhibition of ribosomal S6 kinase triggering an intracellular signaling cascade that releases the pro-apoptotic factor BCL2, an antagonist of cell death [3]. This could induce the activation of the intrinsic apoptotic pathway and ATP depletion, whereas myocyte loss and ATP depletion would lead to left ventricular dysfunction. Sunitinib also mediates the inactivation of AMP-activated protein kinase, which is crucial in cellular response to hypoxia and may affect the survival of cardiomyocytes [3]. Finally, sunitinib-mediated inactivation of AMP-activated protein kinase could promote hypertrophy through increased activity of the eukaryotic elongation factor-2 and the mammalian target of rapamycin [3].

### 1.2.2. Management of heart failure

Management of patients with heart failure according to the NYHA classification is outlined in Fig. 3.

**Asymptomatic patients with LVEF dysfunction (NYHA I).** According to the recent ACC/AHA guidelines, asymptomatic cancer patients treated with potentially cardiotoxic chemotherapy are considered at high risk of heart failure. Modification of risk factors for coronary heart disease, lifestyle changes, and treatment of hypertension are encouraged in these patients [26]. Specific guidelines were published by the United Kingdom National Research Institute for patients receiving Trastuzumab. These recommendations simplify the rules for interrupting the use of trastuzumab in patients with symptoms of heart failure or LVEF dysfunction and encourage the use of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers [52].

Patients developing asymptomatic LVEF dysfunction of <50% during angiogenesis inhibitor therapy should be referred to a cardiologist and should receive angiotensin-converting enzyme (ACE) inhibitors. Angiogenesis inhibitors should be stopped until improvement and normalization of LVEF.

**Symptomatic patients with LVEF dysfunction (NYHA II to IV).** Patients who develop symptomatic heart failure during MTT should be referred to a cardiologist and evaluated with comprehensive echocardiography, which allows the assessment of structural heart disease (ischemic, dilated, and valvular heart disease), and measures LVEF function. When fluid retention is present, patients should initially be treated with IV diuretics and nitrates. Once fluid retention has resolved, ACE inhibitors (e.g. ramipril, captopril, enalapril, lisinopril, trandolapril) should be initiated. Beta-blockers (e.g. bisoprolol, metoprolol, carvedilol, nebivolol) may be initiated 3–4 weeks after the episode of heart failure, once the patient becomes asymptomatic and is in a stable condition. ACE inhibitors and beta-blockers should be initiated at a low dose. Dosage should be gradually increased. The

---

goal is to reach the highest tolerated dose. Renal function, serum potassium concentration, BP, and signs of heart failure should be carefully monitored during titration of ACE inhibitors and beta-blockers. Aldosterone receptor antagonists (e.g. spironolactone) are indicated in NYHA III or IV patients in addition to ACE inhibitors, beta-blockers, and diuretics.

Patients with LVEF dysfunction should be evaluated by coronary angiography or dobutamine stress echocardiography to exclude coronary artery disease, which could lead to specific treatment such as angioplasty or a coronary artery bypass graft. Surgical treatment should be discussed if significant valvular dysfunction (mitral regurgitation or aortic stenosis) is found on echocardiography, provided comorbidities and life expectancy are not prohibitive factors.

1.3. QT-interval prolongation

QT-interval prolongation, which increases the risk of fatal arrhythmia, is associated with cardiac toxicity that can be induced by several novel anti-cancer therapies. QT prolongation has garnered attention because of its risk of malignant cardiac arrhythmia with torsades de pointe and sudden cardiac death [53]. QT interval is measured on the ECG from the beginning of the earliest onset of the QRS complex to the end of the T wave. QT interval effects have been associated with several MTT classes including histone deacetylase inhibitors, multi-targeted TKIs, vascular-disrupting agents, farnesyl protein transferase (FTPase) inhibitors, Src/Abl kinase inhibitors, and protein kinase C inhibitors.

Histone deacetylase inhibitors. Depsipeptide (FK228), a cyclic peptide, is a histone deacetylase inhibitor that has been variably associated with QT prolongation but rarely with sudden cardiac death [54,55]. Piekarcz et al. [54] performed cardiac monitoring of 42 patients treated with depsipeptide in a phase II trial: a median QTc prolongation of 14.4 ms was found following treatment as compared to pre-treatment baseline. ECG changes and QTc prolongation were reversible and generally short-lived. No patients had treatment-related sustained or symptomatic arrhythmia.

Multi-targeted TKIs: sunitinib, vandetanib. Several side effects noted on ECG have been described with sunitinib. It has been shown to induce bradycardia, PR interval prolongation, and QT interval prolongation. However torsades de pointe have been observed in less than 0.1% of sunitinib-exposed patients [56]. In a phase I study of patients with advanced solid tumors, sunitinib was associated with a progressive increase in the QTc interval that continued throughout the 24-h observation period, no patients experienced an effect on the QTc interval greater than grade 2 toxicity [56].

Vandetanib interacts with cardiac ion channels leading to repolarization abnormalities and QTc prolongation [57]. QTc prolongation was noted in 10% of patients receiving vandetanib in a phase I study, but was not associated with any clinical sequela apart from dose interruption or reduction as prophylaxis [58]. In a multicenter phase II trial, asymptomatic grade I QTc prolongation was observed in 20.6% patients at the dose of 300 mg/day [58]. In a phase II trial assessing vandetanib in combination with docetaxel, all episodes of QTc prolongation were asymptomatic and manageable with dose interruption and/or reduction [59]. No patient in the docetaxel group exhibited QTc prolongation, while 4.8% of those receiving vandetanib 100 mg/day plus docetaxel and 11.4% of those on vandetanib 300 mg/day plus docetaxel exhibited QTc prolongation [60]. In patients with nonsmall cell lung cancer, QTc prolongation was found in 15% of patients treated with vandetanib compared to none among control patients [61]. However, no significant QTc interval prolongation was seen in a phase II trial of vandetanib in patients with multiple myeloma [62].

SRC/ABL inhibitors: nilotinib, dasatinib. In a phase I study, 119 patients with imatinib-resistant CML or acute lymphoblastic leukemia received nilotinib orally at doses varying from 50 to 1200 mg once daily. In this population, QTc interval increased by 5–15 ms [63]. In phase I and II studies, QTc prolongation >60 ms was reported in 1.9% and 2.5% patients with chronic- and accelerated-phase CML, respectively, while grade 3/4 drug-related QT prolongation was reported in <3% of cases [64]. Five sudden deaths (0.6%) considered probably or potentially related to nilotinib were reported in a phase II study [65]. A mean QTc increase of 5 ms was found in a phase II study of nilotinib and 1% of patients had a QTc interval >500 ms at day 8 after starting nilotinib [66]. In another phase II trial of nilotinib, 4% of patients exhibited QTc prolongation >60 ms, but none experienced torsades de points or QTc >500 ms [67].

In an analysis of 467 cancer patients receiving dasatinib in phase II studies, mean QTc increased from 3 to 6 ms, with three patients (<1%) showed QTc >500 ms and 14 patients (3%) had a QTc increase >60 ms from baseline [67].

Vascular-disrupting agents. Among 25 patients with advanced cancer receiving combretastatin A4 phosphate (CA4P) in a phase I trial, seven episodes of grade 1 QTc prolongation were observed [68]. Compared to baseline, mean QTc prolongation was 27.2 ms at 3 h and 30.8 ms at 4 h after the administration, while only one patient experienced a QTc >500 ms [68].

FPPase inhibitors. Six episodes of QTc prolongation were documented in a phase I study of L-778123 in 25 patients with solid tumors [69]. One patient experienced a 30% prolongation of QTc interval compared to baseline (from 434 to 563 ms) without any symptoms and five patients presented a QTc prolongation up to 480 ms; QTc normalized in all patients after drug discontinuation [69]. When L-778123 was combined with paclitaxel in a phase I study, 31% of patients experienced minor increases in QTc (<grade 1) [70].

Protein kinase C inhibitors. During phase I trials of advanced cancer patients, enzastaurin induced grade 1 QT prolongation in 6.4% of patients in one study [71] and grade 2 QT prolongation in 6.1% of patients in another study [72].
Baseline ECG, QTc measurement using Bazett or Fridericia formulas

Identify characteristics that place patient at increased risk for QT prolongation

History of QT prolongation or congenital long QT, baseline QT > 500 msec

Begin MTT

Periodic monitoring with ECG at 1 week and following any dose adjustment

Cardiologist expertise

Stop MTT if QTc > 500 msec or QT prolongation > 60 msec

Fig. 4. Management of patients with QT prolongation induced by MTT.

Table 1
Risk factors for drug-induced torsades de pointe.

- Baseline QT prolongation
- Subclinical long QT syndrome
- Female gender, diabetes, cirrhosis
- Myocardial ischemia, congestive heart failure, cardiac hypertrophy, myocarditis, bradycardia, atrioventricular block
- Hypokalemia, hypomagnesemia, hypocalcemia
- Hypothyroidism, hyperparathyroidism, hyperaldosteronism
- Subarachnoid hemorrhage, stroke, intracranial trauma
- Digitalis therapy
- Rapid rate of intravenous infusion with a QT-prolonging drug

1.3.1. Management of QT prolongation

A proposal for the management of QT prolongation is outlined in Fig. 4. Several risk factors and drugs known to be associated with QT prolongation are presented in Tables 1 and 2. In patients receiving angiogenesis inhibitors such factors should be identified before initiating treatment in order to reduce the incidence of QT prolongation and torsades de pointe.

Table 2
Drugs leading to acquired long QT syndromes and torsades de pointe.

- Antiarrhythmic drugs
  - IA: ajmaline, disopyramide, procainamide, quinidine
  - IB: flecainide, propafenone
  - III: amiodarone, sotalol, dofetilide, ibutilide
- Vasodilators: bepridil, perhexiline
- Serotonin agonists/antagonists: cisapride, ketanserin, zimeldine
- Antipsychotics: phenothiazine, droperidol, haloperidol
- Antidepressants: amitryptyline, clomipramine, desipramine, imipramine
- Antimicrobial agents: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin, ketoconazole, miconazole, itraconazole
- Anti-emetic agents: domperidone, chlorpromazine, droperidol
- Anthracyclines (doxorubicin), arsenic
- Methadone

Electrocardiograms should be obtained to monitor QT at baseline, 7 days after the initiation of treatment, and periodically following any dose adjustments. ECGs should be performed periodically during therapy in order to detect asymptomatic prolongation of the QT interval. QT should be measured and corrected (QTc) for heart rate according to Bazett or Fridericia formulas. A baseline QTc > 470 ms in men and 480 ms in women should be considered abnormal and postponed the treatment initiation. The patient should be send to a cardiologist. Treatment should be stopped if the QTc is >500 ms or in case of QT prolongation exceeding 60 ms.

Close monitoring and repletion of electrolytes are needed before treatment initiation and during treatment. Hypomagnesemia and hypokalemia should be corrected prior to treatment initiation. Treatment with CYP3A4 inhibitors should be avoided, particularly in patients receiving sunitinib. In case of torsades de pointe, the offending drug should be stopped and patients should be monitored closely in an intensive care unit. Magnesium infusion and shortening of the QT interval by increasing heart rate are the main urgent therapeutic actions that should be undertaken.

1.4. Cardiac ischemia

Bevacizumab. Combination treatment with bevacizumab and chemotherapy, is associated with and increased risk of arterial thromboembolism (myocardial and cerebrovascular events) compared with chemotherapy alone. In a post hoc analysis of randomized controlled trials that evaluated combination treatment with bevacizumab and chemotherapy versus chemotherapy alone in 1745 patients with metastatic colorectal, breast, and nonsmall-cell lung cancer, Scappaticci et al. [73] found that combined treatment with bevacizumab and chemotherapy was associated with increased risk for...
Before starting MTT agents
Cardiovascular risk at baseline

Referral to cardiologist for:
- Cardiovascular monitoring
- Identification and management of previous cardiac disease
- Discussion on benefit/risk of MTT agents

Unstable coronary artery disease
Uncontrolled hypertension
Acute heart failure
Heart rhythm disorders
Pulmonary embolism

Normal

Start MTT agents

Repeat visit for cardiologic follow-up
Clinical examination including BP measurement, Holter EKG, cardiac ultrasound, BNP, troponin

Abnormal

an arterial thromboembolic event (hazard ratio [HR] = 2.0; 95% CI = 1.05–3.75; P = .031) compared with chemotherapy alone. The absolute rate of developing arterial thromboembolism was 5.5 events per 100 person-years for those receiving combination therapy and 3.1 events per 100 person-years for those receiving chemotherapy alone (HR = 1.8; 95% CI = 0.94–3.33; P = .076). Development of an arterial thromboembolic event was associated with a prior arterial thromboembolic event (P < .001) or age of ≥65 years (P = .01).

Sunitinib and sorafenib. A higher frequency of arterial thrombotic events, particularly myocardial ischemia, were found in patients receiving sorafenib for metastatic renal cancer [74] compared to placebo (3% vs 1%, respectively; P = .01). No significant increase of acute coronary syndrome or myocardial ischemia was found between patients receiving sunitinib and placebo.

Cardiac troponin I is a marker of myocardial injury and necrosis that is used to diagnose and stratify patients suffering from acute coronary syndrome. It has also been used as a marker of myocardial damage, particularly in patients receiving chemotherapy that includes an anthracycline. In a single-center observational study, Schmidinger et al. [8] found a higher rate of thromboembolic events with sunitinib and sorafenib than previously reported. They found that 24% and 12% of patients receiving sunitinib and sorafenib, respectively, exhibited abnormal troponin levels during follow-up.

Chu et al. [4] found that 17.6% of patients receiving sunitinib exhibited abnormal troponin levels.

Vascular-disrupting agents. The cardiovascular safety profile of CA4P has been evaluated in a phase I study of 25 patients with advanced solid tumors: 8% of patients had ECG changes and a troponin increase consistent with acute coronary syndrome within 24 h of CA4P infusion [75].

Several cardiovascular events such as myocardial ischemia, transient asymptomatic hypotension, transient cerebral ischemia, and asymptomatic ventricular tachycardia were observed in patients treated with the combretastatin A4 analogue, AVE-8062, leading to the temporary interruption of the study [75]. However, since no vascular events had been observed in the three weekly schedule study, up to a dose of 22 mg/m², this trial was later resumed at that dose, with restricted eligibility criteria and increased cardiovascular monitoring (continuous 24-h ECG, continuous ambulatory BP, serial CPK, troponin, ECG, ventriculography, and echocardiogram) [76,77].

2. Conclusion

Oncologists and cardiologists should remain vigilant regarding the risks for cardiovascular disease in patients receiving MTT. It is important that oncologists understand the need to adequately assess cardiac function and vascular risk because many patients with cancer are more likely to die of heart disease than cancer [78]. Similarly, it is also necessary to alert cardiologists about the increased risk for cardiovascular events in the cancer patient population and educate them on how to deal with them. A clinical endpoint for patients with cancer, particularly those at high risk for a cardiovascular event, should be the prevention and optimal management of cardiovascular risk factors. A proposal for patient evaluation prior to and during MTT is outlined in Fig. 5, however cardiological referral can be envisioned even earlier. Patients should be encouraged to follow standard guidelines for reduc-
ing cardiovascular risk. BP control, lipid level reduction, and lifestyle modifications to include exercise and smoking cessation are suggested for prevention, and early identification of cardiovascular disease should be undertaken. This approach involves the patient’s primary care physician, the oncologist, and the cardiologist. The goals of the multidisciplinary management of the cancer patient are to improve clinical outcomes maximize consistency, continuity, coordination, and cost-effectiveness of treatment and to foster better communication among clinicians [79,80]. Furthermore, increased communication between a patient’s oncologist, primary care physician, and cardiologist will help ensure proper management of cardiovascular risk factors, appropriate follow-up care, and risk-reduction interventions for the prevention of cardiovascular events associated with the use of chemotherapeutic regimens commonly used to treat cancer.


generates an auxiliary contract for the purpose of personal data protection and data transfers associated with the works and projects developed within the framework of the program. This contract is under the direction of the National Research Council of Canada. The purpose of this contract is to ensure the confidentiality of the personal information collected in the context of the research projects, and to comply with the requirements of the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada.


generates an auxiliary contract for the purpose of personal data protection and data transfers associated with the works and projects developed within the framework of the program. This contract is under the direction of the National Research Council of Canada. The purpose of this contract is to ensure the confidentiality of the personal information collected in the context of the research projects, and to comply with the requirements of the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada.


generates an auxiliary contract for the purpose of personal data protection and data transfers associated with the works and projects developed within the framework of the program. This contract is under the direction of the National Research Council of Canada. The purpose of this contract is to ensure the confidentiality of the personal information collected in the context of the research projects, and to comply with the requirements of the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada.


[43] Cottrite P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in...


Biographies

**Stephane Ederhy** is a cardiologist in the department of cardiology at Saint Antoine Hospital (Paris, France). He is specialized in ultrasound echocardiography. Dr Ederhy has focused on the application of new technologies such as speckle tracking imaging to evaluate the cardiac complications of molecular targeted agent.

**Jean-Charles Soria** is a Professor of Medicine and Medical Oncology at South-Paris University. He is a tenure-track and full time cancer specialist at Institut Gustave Roussy. Dr Soria trained as a medical oncologist and obtained the Silver medal from Paris Medical School in 1997. He gained a PhD degree in the fundamental basis of oncogenesis in 2001, and completed his training with a two-year post-doctoral fellowship in the Department of Thoracic Head and Neck Medical Oncology at MD Anderson Cancer Center, Houston, USA.

Professor Soria is currently head of the phase I program at Institut Gustave Roussy and is a member of the lung cancer unit with a focus on targeted therapies. His main research interest are: early clinical development, phase I trials across solid tumors, pharmacodynamic biomarkers, lung cancer. He is also involved in translational research aspects related to tumor progression notably in lung cancer models (INSERM unit 981). Dr Soria was a member of ESMO executive committee from 2008 to 2009, and serves as an ASCO committee member since 2006. He has contributed to over 210 peer-reviewed publications, including publications as first or last author in the New England Journal of Medicine, the Journal of the National Cancer Institute, and the Journal of Clinical Oncology.