Cardiovascular complications of metastatic colorectal cancer treatment

Kalliopi Keramida[1,2], Georgios Charalampopoulos[3], Dimitrios Filippiadis[3], Elias Tsougos[4], Dimitrios Farmakis[1,2]

[1]Cardio-Oncology Clinic, Heart Failure Unit, Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece; [2]University of Cyprus Medical School, Nicosia, Cyprus; [3]2nd Radiology Department, Attikon University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece; [4]2nd Department of Cardiology, Heart Failure and Preventive Cardiology Section, Henry Dunant Hospital, Athens, Greece

Contributions: (I) Conception and design: K Keramida, D Filippiadis; (II) Administrative support: D Farmakis, G Charalampopoulos; (III) Provision of study materials or patients: K Keramida; (IV) Collection and assembly of data: K Keramida; (V) Data analysis and interpretation: E Tsougos, K Keramida, G Charalampopoulos; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Kalliopi Keramida. University of Cyprus Medical School, Shakolas Educational Center for Clinical Medicine, Palaios dromos Lefkosias Lemesou 215/6, 2029 Aglantzia, Nicosia, Cyprus. Email: keramidakalliopi@hotmail.com.

Abstract: Colorectal cancer (CRC) is the third most common malignancy in men and the second in women and the fourth cause of cancer death. Survival rates decrease greatly according to the stage of the disease at the time of diagnosis. Approximately 50% of CRC patients will develop metastatic disease (mCRC) with survival and prognosis depending on the timing of metastatic development, and the localization and number of metastatic sites. The overall survival of patients with mCRC has been significantly improved over the last years from approximately 12 to more than 30 months with the integration of multiple cytotoxic agents and targeted therapies. The optimal therapeutic strategy depends on the general condition and performance status of the patient, the resectability or not of metastases and the mutational status of the tumor in terms of *BRAF* and *RAS*. Cardiovascular (CV) complications of mCRC treatment may develop peri-operatively and mostly during chemotherapy. During first-line treatment, 90% of patients experience more than one adverse event (AE) and 39% of them are CV. Angina, hypertension, arrhythmias, arterial and venous thrombotic events (VTEs), heart failure (HF) and death are the main CV events resulting from the applied chemotherapy regimens. Cardio-oncology consultation for identification of high-risk patients, proper monitoring during and after therapy and timely intervention would allow the successful prevention and the efficient management of cardiotoxicity, rendering the patient able to receive the indicated cancer therapy and improving the overall outcome.

Keywords: Colorectal cancer (CRC); cardiotoxicity; chemotherapy; antimetabolites; tyrosine kinase inhibitors (TKIs); angiogenesis inhibitors

Colorectal cancer (CRC) burden

CRC is one of the most prevailing malignancies, being the third most commonly occurring cancer in men, and the second in women (1,2), making up about 10% of all cancer cases (3). It is the fourth highest cause of cancer death (1).

Its incidence increases with increasing age (4). It is more prevalent in developed countries, where more than 65% of cases are found (3). The global burden of CRC is expected to increase by 60% to more than 2.2 million new cases and 1.1 million cancer deaths by 2030 (1).

Approximately 95% of CRC cases concern

adenocarcinomas, while the rest include mucinous carcinomas and adenosquamous carcinomas (1). The relative survival rate for CRC is 65% at 5 years following diagnosis and 58% at 10 years (5). Survival rates decrease greatly according to the stage of the disease at the time of diagnosis. Only 39% of CRC patients are diagnosed with localized-stage disease, for which the 5-year survival rate is 90%, while it declines to 14% for metastatic disease (mCRC) (6).

Approximately 50% of CRC patients will develop metastatic disease (7). The most common sites for metastasis for CRC are the liver and the thorax, followed by the peritoneum, the bones and the nervous system (8). The timing of metastases development (synchronous *vs.* metachronous at the time of diagnosis), their localization (e.g., peritoneal or distant lymph node metastases) and the number of metastatic sites affect crucially the prognosis (9).

The therapeutic approach for mCRC is based on the use of combination cytotoxic therapy that has led to a critical improvement of survival from approximately 1 year during the era of fluoropyrimidine monotherapy to more than 30 months with the integration of multiple cytotoxic agents and targeted therapies (10).

The factors that determine the optimal therapeutic strategy for each mCRC patient are the general condition and performance status, the resectability or not of metastases and the mutational status in terms of *BRAF* and *RAS* (11,12). First line therapy in fit patients includes surgery probably with peri-or post-operative chemotherapy, including fluopyrimidines, irinotecan, oxaliplatin, monoclonal antibodies, regorafenib and trifluridine/tipiracil. Alternatively, radiation and local ablation techniques can be used according to the sites of metastases (11,12).

During the first treatment of mCRC, 90% of patients experience more than 1 adverse event (AE) and 39% of them are cardiovascular (CV), followed by AEs from the central nervous system, endocrine/metabolic, respiratory and finally hematologic (13).

CV complications of metastatic CRC treatment

CV complications of mCRC treatment may develop during or after surgery and mostly during chemotherapy (*Table 1*). Peri-operative CV complications, including acute myocardial infarction (MI), heart failure (HF) and CV death, rise with patients' age (14,15), highlighting the impact of frailty and making the optimization of CV status of elderly patients with multiple comorbidities imperative.

Antimetabolites

5-fluorouracil (5-FU)

Fluopyrimidines, including intravenous 5-FU and oral capecitabine, constitute the typical backbone of chemotherapeutic regimens for mCRC (11). 5-FU belongs to antimetabolites, and it is a pyrimidine analogue acting through the irreversible inhibition of thymidylate synthase. The combination of 5-FU with other cytotoxic agents, such as irinotecan and oxaliplatin, has improved the survival of patients with metastatic disease (16). The reported incidence of 5-FU cardiotoxicity varies from 1.2% to 18% (17). This significant variability can be explained by the dose and method of administration, the combination with other cardiotoxic medications, the concurrent radiotherapy and most importantly by the pre-existing CV conditions and risk factor profile.

Angina, is the most common clinical presentation of 5-FU-induced cardiotoxicity (17), followed by dyspnea, palpitations and hypotension (18). Electrocardiographic (ECG) changes such as ST segment changes, right bundle branch block (RBBB), arrhythmias, including atrial fibrillation (AF) (19), myocarditis (20) and pericarditis (21), acute MI (22), apical ballooning syndrome (23), cardiogenic shock, HF (24) and even death (25) have also been described.

Cardiotoxicity from 5-FU occurs most commonly during the first cycle (25). It can occur anytime during infusion or up to 1–2 days after, with the vast majority of cases presenting within the first 72 h and usually not later than the first 3 cycles (17). The median time to initiation of symptoms is 12 h following initiation of the infusion initiation (23). Symptoms and ECG changes may resolve soon after drug discontinuation, but cardiac complications due to 5-FU have been described up to one month after the drug discontinuation (26).

The pathogenesis of 5-FU induced cardiotoxicity has not yet been fully elucidated. Endothelial injury leading to vasoconstriction, procoagulant state and direct myocardial toxicity are the main proposed mechanisms (27). The most popular mechanism however is coronary vasospasm. Anginal pain, ST changes and troponin elevation have been developed in patients without occlusive macrovascular coronary disease (CAD) (26). A plausible explanation could be microvascular dysfunction. Dihydropyrimidine dehydrogenase (DPD) deficiency is another presumable though controversial mechanism of severe forms of 5-FU cardiotoxicity (28).

Table 1 Cardiotoxic effects of chemotherapies used for metastatic colorectal cancer

Therapy	Cardiotoxic effect
Antimetabolites	
5-FU	Angina
	Dyspnea
	Arrhythmias
	Hypotension
	Myocarditis
	Pericarditis
	MI
	Apical ballooning syndrome
	HF
	Cardiogenic shock
	Death
Capecitabine	Angina
	Arrhythmias
	Acute coronary syndromes
	HF
	Sudden cardiac death
Monoclonal antibodies	
Bevacizumab	Hypersensitivity reaction
	Hypertension
	HF
	ATEs
	Venous thromboembolic events
Cetuximab	Hypersensitivity reaction
	Angina
	Acute coronary syndrome
	Heart failure
	Shock
	Sudden cardiac death
Panitumumab	Palpitations/arrhythmias
	Chest pain
	Hypersensitivity reaction
	Hypotension
	Hypertension
	Electrolytic disorders
	Venous thromboembolic events

Table 1 (*continued*)

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Therapy	Cardiotoxic effect
Tyrosine kinase inhibitors	
Regorafenib	Hypertension
	Acute coronary syndromes
VEGF biologic inhibitors	
Aflibercept	Hypertension
	Heart failure
	ATEs
	Venous thromboembolic events

5-FU, 5-fluorouracil; MI, myocardial infarction; HF, heart failure; ATEs, arterial thromboembolic events; VEGF, vascular endothelial growth factor.

Data concerning the predisposing factors for the 5-FU induced cardiotoxicity are inconclusive regarding CV risk factors and cardiac comorbidities (25). However previous thoracic irradiation, previous treatment with cardiotoxic drugs and combination therapy with cisplatin increase the risk of developing cardiotoxicity.

The management of 5-FU cardiotoxicity depends on the clinical presentation and the severity of symptoms and comprises of 4 steps: (I) immediate discontinuation of 5-FU; (II) empirical treatment of symptoms; (III) confirmation of the causal relationship of symptoms with 5-FU and (IV) rechallenge with pharmacological prophylaxis or determination of alternative chemotherapeutic regimens. Since 5-FU cardiotoxicity can be potentially fatal, immediate discontinuation of the treatment and initiation of antianginal therapy with calcium channel blockers (CCBs) or nitrates is the only treatment suggested officially by the European Society of Cardiology (ESC) (29). This leads to improvement of symptoms in 69% of affected patients (25). In cases of severe or life-threatening CV or cerebral toxicity, uridine triacetate can be used as an antidote for fluoropyrimidines (30). This oral pyrimidine analogue of uridine, approved by the American Food and Drug Administration (FDA) in 2015, acts competing with the toxic fluorouridine triphosphate (FUTP), one of the main metabolites of 5-FU, for incorporation into RNA in normal tissues, providing protection from its toxic effects. Afterwards, it is critical to attribute the cardiac symptoms to 5-FU within reasonable degree of certainty, using mostly clinical judgment and/or laboratory tests. Unnecessary withholding of effective chemotherapy could jeopardize

the patient's chance of cure, while re-challenge could be life threatening. Obstructive CAD should be excluded with invasive or non-invasive tests according to the level of CV risk and should be treated accordingly. Finally, the use of alternative chemotherapeutic regimens is possible in mCRC, with irinotecan alone, irinotecan plus oxaliplatin, cetuximab or panitumumab (for patients with *RAS/BRAF* wild-type tumors) or with trifluridine-tipiracil, regorafenib and ramucirumab or raltitrexed alone or in combination regimens (31).

Capecitabine

Capecitabine, a fluoropyrimidine derivative, was developed with the aim of providing a more effective and less toxic alternate to 5-FU (32). It can substitute intravenous 5-FU as a single agent or it can be combined with oxaliplatin, with the convenience of oral administration in the first-line treatment of mCRC (11). Capecitabine is the oral prodrug of 5-FU. It can lead to prolonged exposure of tumor tissue to the active drug, mimicking continuous infusion of 5-FU, while maintaining very low plasma levels, leading possibly to significantly less serious and less frequent toxicity than 5-FU when used alone or in combination with other cytotoxic agents (32). Angina-like chest pain, acute ischemic events (33), HF and arrhythmias, such as AF (34) and/or ventricular fibrillation (35), sudden cardiac death attributed possibly to coronary vasospasm have been reported with capecitabine (36), similarly to 5-FU. The highest incidence of these events is recorded when the patients receives combined therapy with capecitabine, oxaliplatine and bevacizumab (36) and occur mostly during the first cycle (37). The management is symptomatic, while re-challenge does not seem an attractive and safe option (25). S-1, an oral fluoropyrimidine, consisting of tegafur, a 5-FU prodrug, oteracil potassium and gimeracil, which inhibits the degradation of 5-FU by DPD inhibition, can be possibly administered safely after capecitabine or 5-FU induced cardiotoxicity according to a limited number of case reports (38).

Monoclonal antibodies

Bevacizumab

Monoclonal antibodies are another class of medications that is recommended as first and second-line treatment of mCRC (11). Bevacizumab, cetuximab and panitumumab are approved for mCRC (11). Bevacizumab is the first angiogenesis inhibitor that has been approved by the FDA since 2004 for the treatment of mCRC (39). It is a humanized IgG monoclonal antibody targeting circulating vascular endothelial growth factor A ligand (VEGF-A) that plays a crucial role in regulating angiogenesis in cancer cells. It has been approved as part of combination regimens containing 5-FU/capecitabine, oxaliplatin, leucovorin and irinotecan (FOLFOX/CAPOX/FOLFIRI or FOLFOXIRI) or with fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment (11), resulting in higher median overall survival.

Cardiotoxicity of bevacizumab comprises of class effects and specific to this substance effects. A hypersensitivity reaction that can even be fatal with hypotension, dyspnea, fever and hypoxia is the most serious class effect and is due to the massive release of cytokines. The other two class effects are hypertension, the most frequent side effect of bevacizumab, and HF. The proposed responsible molecular mechanisms for the development of hypertension or the worsening of pre-existing hypertension include rarefaction of neovascularization, an imbalance in neurohormonal factors, endothelial dysfunction with reduction of vascular nitric oxide production (40) and renal dysfunction (41). Hypertension is reversible and dependent on the duration of exposure and dose (42). The timing of hypertension occurrence varies from 1 (43) to 6 months (44) after the treatment initiation. Severe hypertension (>200/110 mmHg) is reported in 5–36% of patients but cases of hypertensive emergencies with encephalopathy or subarachnoid hemorrhage are rare. Risk factors for developing bevacizumab-induced hypertension are age >65 years, body mass index (BMI) ≥25, pre-existing hypertension (45), smoking and hypercholesterolemia (46). It is suggested that routine monitoring of blood pressure (BP) must be performed every week during the first cycle, every 2–3 weeks afterwards and then at least once before every administration (41). The treatment should be individualized and usually includes angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) and dihydropyridine CCBs; diltiazem, verapamil are not recommended due to CYP3A4 inhibition, which is also the case for bevacizumab (41,45). Interestingly, it has been suggested that bevacizumab-induced hypertension may be predictive of antitumor efficacy and better survival (47), especially if occurring during the first 3 months.

HF is the third-class effect due to direct myocardial damage. Its incidence is very low in mCRC (1.3%) (48). The underlying mechanism has not been clarified, but hypertension induced by bevacizumab and the effect of blockade of VEGF to the repair of myocardial damage and

collateral vessel formation may play a role (49). Standard HF treatment is applied, including neurohormonal inhibitors.

The most specific CV complication of bevacizumab is increased thromboembolic risk. Arterial thromboembolic events (ATEs) are defined by the National Cancer Institute's Common Toxicity Criteria as myocardial ischemia or MI, cerebral infarction, cerebrovascular accident, cerebral ischemia, ischemic stroke, and peripheral or visceral ATEs (50). It is not clear whether ATEs are dose-related, as studies show controversial results (51). ATEs can occur at any time during treatment, with a median time of 3 months after treatment onset (52). Risk factors for ATEs are age >65 and past history of ATE, while prophylactic aspirin (≤375 mg) decreases the risk, without increasing bleeding events (52).

Venous thrombotic events (VTEs) induced by bevacizumab include deep vein thrombosis (DVT), pulmonary embolism (PE) and thrombophlebitis. However, the added risk of bevacizumab to VTEs is ambiguous, since cancer patients are a high-risk group (51,53). Oral anticoagulation is indicated and does not seem to increase the bleeding risk (54).

Cetuximab and panitumumab

Cetuximab and panitumumab are monoclonal antibodies that bind to the human epidermal growth factor receptor (EGFR) and can be used as first, second or third-line treatment in mCRC in different combinations in *RAS*-wild type and *BRAF* type patients (11). They can be used with 5-FU and oxaliplatin or irinotecan (FOLFOX, FOLFIRI) as first-line treatment, with 5-FU and irinotecan (FOLFIRI) as second-line and with irinotecan alone as third-line regimens (11). However, they should not be used with capecitabine or bolus 5-FU-based regimens (11). Cetuximab is a human/mouse chimeric monoclonal antibody that competitively binds to EGFR resulting in receptor internalization; it improves survival when added to other chemotherapeutic regimes (55). It can cause allergic reactions that can be severe (2–5%) and fatal (<0.1%), usually during the first hour of the first administration and sometimes also hours afterwards or during subsequent infusions. Urticaria and bronchospasm can be accompanied by hypotension and in rare cases by angina, MI, HF, shock and sudden death (56). Cetuximab may also lead to increased risk of VTEs (57) but the data are limited. Panitumumab is a fully human monoclonal IgG2 antibody produced in a mammalian cell line by recombinant DNA technology. Panitumumab has been reported to cause hypomagnesemia, hypokalemia, dehydration,

hypotension, hypertension and VTEs (58). Cetuximab and panitumumab have a similar CV toxicity profile, with the most common cardiac events requiring treatment being palpitations/arrhythmias (25.8%), chest pain (8.1%), arrhythmias (4.8%) (59) and dyspnea (60).
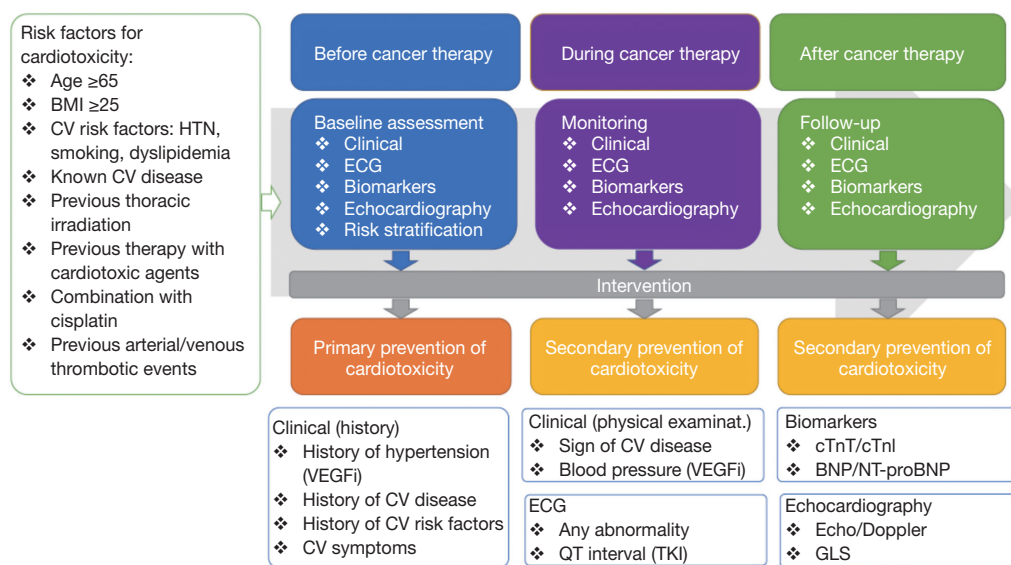
Tyrosine kinase inhibitors (TKIs)

Regorafenib

Regorafenib is a multi-kinase inhibitor that targets VEGF receptors 1–3, KIT, PDGFR-alpha, PDGFRbeta, RET, FGFR-1 and FGFR-2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and ABL, involved in angiogenesis and oncogenesis (61,62). Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS*-wild-type patients with EGFR antibodies, according to ESMO consensus guidelines for mCRC (11). It is relatively safe concerning CV AEs, with the most frequent being hypertension. The reported incidence rates of all-grade and high-grade hypertension are 44.4% and 12.5%, respectively (63). It is noteworthy that the incidence of hypertension is highest in cycle 1 and tapered to low or no incidence over cycles 2 to 8 (64). Hypertension typically resolves after cessation of the drug and its treatment is not based on specific evidence-based guidelines. Diuretics should be avoided as they may worsen dehydration, especially if the patient also experiences regorafenib-induced diarrhea. For resistant grade 3 hypertension, regorafenib dose should be reduced, while for grade 4, regorafenib should be held till BP levels return to grade 2 or normal (65). However preventive strategy is more important, and it is crucial to identify and treat hypertension before initiation of regorafenib therapy. Then BP monitoring by a healthcare professional at a weekly basis is useful for the first two cycles of therapy. Thereafter, patients should be encouraged to measure their BP at home daily (65).

Myocardial ischemia and infarction are rare adverse cardiac effects of regorafenib by unclear pathophysiological mechanisms (64).

Newer agents

Trifluridine/tipiracil (TAS-102) belongs to fluoropyrimidines and is another new option in patients with mCRC and pre-existing cardiac disease, pretreated with all active drugs and biologics, that can be used instead of regorafenib with better safety profile (11,66). TAS-102, is well tolerated and does not

Figure 1 Cardio-oncology consultation in patients with metastatic colorectal cancer. BMI, body mass index; CV, cardiovascular; HTN, hypertension; ECG, electrocardiographic; TKI, tyrosine kinase inhibitors; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro b-type natriuretic peptide; VEGFi, inhibitors of vascular endothelial growth factor; GLS, global longitudinal strain; Echo, echocardiogram.

appear to have any cardiac toxicity (31,66).

Aflibercept also known as ziv-aflibercept or VEGF-Trap, is an intravenously administered, fully human, recombinant fusion protein that blocks the activity of soluble VEGF-A, VEGF-B, and PIGF (placental growth factor) by acting as a ligand trap, thus inhibiting the growth of new blood vessels that supply oxygen and nutrients to tumors dependent on VEGF pathways (67). Aflibercept is approved in combination with FOLFIRI as second line treatment in mCRC that is resistant to or has progressed after treatment with an oxaliplatin-containing regimen (68). It is associated with significantly longer progression-free survival with acceptable tolerability (69). The most frequent cardiotoxic effect of aflibercept as a VEGF inhibitor is hypertension (69), while HF, ATEs and VTEs are uncommon (70). The incidence of all-grade hypertension ranges between 16.7% and 51.4%, while of high-grade hypertension from 6.3% to 27.3 % (71). Half of the cases of aflibercept-induced hypertension develop during cycles 1–5 (70) and there is no association with the BP levels before its administration (72). Since uncontrolled, severe hypertension induced by aflibercept could lead to serious CV complications such as hypertensive encephalopathy, central nervous system hemorrhage, HF and ATEs (73), early diagnosis and treatment is essential for outcome. Blood pressure monitoring after initiation of therapy with aflibercept

is almost obligatory, but there are no specific guidelines concerning treatment. Permanent discontinuation of aflibercept is suggested in patients with hypertensive crisis or hypertensive encephalopathy and temporal suspension in cases with severe hypertension that is not controlled with medical management (71).

Newer therapeutic options, such as the combination of veliparib, a poly (adenosine diphosphate ribose) polymerase (PARP) inhibitor and temozolomide, a potent DNA-alkylating agent is well tolerated in patients with advanced, refractory to all the aforementioned therapies mCRC (74) with good tolerability and safety profile.

Cardio-oncology consultation

Figure 1 outlines the scheme of cardio-oncology consultation in patients with mCRC. The main aims of cardio-oncology consultation are to render the cancer patient fit to receive the indicated cancer therapy, to minimize the risk of cardiotoxicity, and if cardiotoxicity occurs, to diagnose it early to allow its proper and timely management. Patients with risk factors for cardiotoxicity are referred to the Cardio-oncology clinic before cancer therapy (75). Baseline assessment at the Cardio-oncology clinic consists of clinical evaluation and ECG and, if deemed necessary, echocardiography and cardiac biomarkers

(troponin and/or natriuretic peptides) to identify possible CV disease or risk factors and to stratify the risk of cardiotoxicity. If necessary, treatment of CV disease or modification of risk factors is applied. The type and frequency of subsequent Cardio-oncology monitoring during and after cancer is scheduled according to initial risk stratification.

Conclusions

The overall survival of patients with mCRC has been significantly improved over the last years from approximately one year to more than 30 months in recent clinical trials with the integration of multiple cytotoxic agents and targeted therapies. Some of these regimens may lead to the development of cardiotoxic events, jeopardizing patients' life, quality of life and chance to survive if therapy has to be discontinued. The earlier recognition of CV AEs is a key element to proper treatment and to suitable adjustment of the regimen used, if needed.

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Footnote

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