Cancer treatment has improved extraordinarily in recent years. The development of targeted therapies has widened the cardiotoxic spectrum of antineoplastic drugs. Optimum management of cardiovascular disease before and during antineoplastic treatment is essential to reduce morbidity and mortality in cancer patients. This article reviews the incidence and characteristics of cardiotoxic effects of antineoplastic drugs with special focus on the pathophysiological mechanisms. It also emphasizes the importance of early detection and correction of cardiovascular risk factors and the relevance of close cardiac monitoring during antineoplastic treatment in order to reduce cardiotoxicity.

Key words: adverse effects, antineoplastic agents, arrhythmia, chemically induced heart diseases, heart failure, QTc prolongation

introduction

Cardiotoxicity is defined by the National Cancer Institute as the 'toxicity that affects the heart'. This definition includes a direct effect of the drug on the heart but also an indirect effect due to enhancement of haemodynamic flow alterations or due to thrombotic events [1]. Cardiotoxicity has a rising relevance as a consequence of the global improvement in cancer management, which leads to better survival and, therefore, adverse effects of treatments have significant consequences on patient outcome [2–4]. New targeted therapies have widened the cardiotoxic spectrum of antineoplastic drugs.

The aim of this article is to describe the incidence and the underlying mechanisms of cardiotoxicity induced by antineoplastic drugs focusing on targeted therapies, as well as strategies to prevent and treat this spectrum of toxic effects. Drugs will be classified based on their main cardiotoxic effect: left ventricle dysfunction, rhythm disturbances and ischaemia.

left ventricle dysfunction

anthracyclines

Anthracycline-associated cardiotoxicity (AAC) can be divided into three forms: immediate pericarditis–myocarditis syndrome, an early-onset chronic progressive form and a late-onset chronic progressive form. The latter two forms are the most frequently observed [4, 5].

The main risk factor for AAC is the cumulative dose [5]. Other described factors include administration schedule, mediastinal radiotherapy, combination therapy, old age or age <4 years, female gender, ethnicity, hypertension, previous cardiovascular disease, chromosomal abnormalities and liver disease [5].

The main hypothesis for the underlying mechanism of AAC is the generation of reactive free radical species that interact and damage cellular membranes. Other possible mechanisms are the induction of apoptosis, mitochondrial DNA damage, changes in ATP production, downregulation of mRNA expression for sarcoplasmic reticulum calcium ATPase [5].

Early interventional treatment with angiotensin-converting enzyme (ACE) inhibitors and β-adrenergic blocking drugs has shown a clear benefit in adult patients with decreased left ventricle ejection function (LVEF) not specifically caused by anthracycline therapy [4]. The potential role of preventive interventions, such as dexrazoxane treatment, will be discussed later in this article.

trastuzumab

Trastuzumab is a humanized monoclonal antibody against the HER2 tyrosine kinase receptor. The incidence of LVEF decrease or asymptomatic heart failure (HF) is ~7% (Table 1), but it can rise to 13% when trastuzumab is administered with concurrent paclitaxel and to 27% with concurrent anthracyclines [6, 7].

The risk factors described for the development of trastuzumab-induced cardiotoxicity include age >50 years, borderline LVEF before trastuzumab treatment, history of cardiovascular disease, cardiovascular risk factors such as diabetes, dislipidemia or elevated body mass index (>30), sequence in which chemotherapy is administered and prior treatment with anthracyclines (cumulative doses >300 mg/m²) [4, 7–10]. Possibly, genetic background and immune status may also have an influence in patient susceptibility to trastuzumab-induced cardiotoxicity [10].

Some differences can be established between anthracycline- and trastuzumab-induced cardiotoxicity: trastuzumab-induced cardiotoxicity is at least reversible while anthracycline-induced is not; there are no ultrastructural changes in cardiomyocytes in...
trastuzumab-induced cardiotoxicity while in anthracycline cardiotoxicity changes such as vacuolization on cardiomyocytes or loss of cardiomyocytes are present [10, 11].

Pathophysiology. HER2 has a relevant role in embryonic heart development. It forms heterodimers with HER4 after the union of neuregulin 1 with HER4 (neuregulins are peptide ligands of HER3 and HER4 expressed only in cardiac tissue). HER2–HER4 heterodimerization leads to its autophosphorylation, which activates several signalling pathways such as Src–FAK, which increases cell–cell contacts and mechanical coupling [12], or phosphatidylinositol 3-kinase (PI3K)–Akt and mitogen-activated protein kinase (MAPK), which promote cardiomyocyte proliferation, survival and contractile function [13]. HER2, HER4 and neuregulin 1 have been shown to be indispensable for heart development as deletion of one of them is lethal in mice embryos [10].

Lapatinib, an oral dual kinase inhibitor of epidermal growth factor receptor (EGFR) and HER2, has been shown to produce a lower rate of cardiotoxicity (1.6%) [14]. Several mechanisms have been described to explain the difference in cardiotoxicity rates between trastuzumab and lapatinib [10]. First, an immune-modulating effect can be raised as trastuzumab has been shown to stimulate antibody-dependent cell-mediated toxicity against HER2 tumour cells in vitro [15]. Second, the pharmacokinetic difference in the duration or extent of inhibition of HER2 by trastuzumab or lapatinib could partially explain these differences, although some studies indicate that the kinetics of HER2-signalling inhibition is similar after a single dose of either agent [10]. A third mechanism has been studied with various anti-HER2 antibodies in rat cardiomyocyte models. The binding of anti-HER2 antibodies to HER2 also triggers BCL-XL downregulation and BCL-XL activation, which leads to loss of mitochondrial membrane potential, reduction in ATP levels, cytochrome C release and caspase activation. The intrinsic resistance of cardiomyocytes to apoptosis induced by the BCL pathway may explain the lack of ultrastructural changes in trastuzumab-induced cardiotoxicity. In this way downregulation of BCL-XL and activation of BCL-XL would lead to ATP depletion and contractile dysfunction [16, 17].

ABL inhibitors: imatinib, dasatinib, nilotinib. Imatinib is a tyrosine kinase inhibitor of ABL, ABL-related gene (ARG), platelet-derived growth factor receptor (PDGFR) α and β and KIT. It binds to the unphosphorylated form of ABL preventing its phosphorylation and therefore inactivating it. Nilotinib has a similar inhibition spectrum but its potency at inhibiting BCR-ABL is 20-fold greater. Dasatinib also inhibits Src family kinases and can inhibit phosphorylated and unphosphorylated ABL, which gives it a greater potency (100-fold greater) [10].

Kerkela et al. [3] initially described 10 cases of congestive heart failure in patients with chronic myelogenous leukaemia treated with imatinib. Later on, a retrospective review of the six registration trials was conducted and the incidence of HF was established as 0.5% out of 2327 patients [18]. The major limitation of this study is the absence of pre-planned cardiac monitoring. During a phase III dose-optimization study with dasatinib in patients with chronic myeloid leukaemia the incidence of HF was 4% [4].

The proposed mechanism of cardiotoxicity [3] of these compounds is related to the activation of the endoplasmic reticulum (ER) stress response, a mechanism that protects cells by shutting down general protein translation while upregulating the expression of specific protective stress response genes. This phenomenon is mediated by PKR like ER kinase (PERK), which phosphorylates the transcription factor eIF2α and activates the IRE1 signalling pathway. Imatinib also leads to an increase in PKCδ expression. Ultimately, prolonged ER stress response and PKCδ expression lead to apoptosis. It has been recently indicated that ER stress response and apoptosis induced by imatinib may occur at concentrations higher than the therapeutic concentration [19].

Sunitinib. Sunitinib is an oral inhibitor of vascular endothelial growth factor receptor (VEGFR) 1–3, PDGFRα/β, KIT, FMS-related tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF1R) and rearranged during transfection (RET). The incidence of HF related to sunitinib in clinical trials ranges from 4% to 11% [20, 21], but the incidence in the general population may be higher (up to 33.8% in renal cancer patients) [22, 23]. The main cause of these discrepant rates may be related to the higher number of co-morbidities in the general population (higher rate of hypertension and previous cardiac ischaemia).

The mechanism of sunitinib-induced cardiotoxicity is an off-target effect due to ribosomal StKinsase inhibition producing ATP depletion that activates the intrinsic apoptotic pathway. It is also known that VEGF signalling is necessary to obtain an adequate response of cardiomyocytes to pressure load in those patients with hypertension, which may explain the higher rate of HF in this population [10].

other targeted therapies

Bortezomib. The incidence of HF with bortezomib, a proteasome inhibitor, is ~5%. The underlying mechanism of HF is the induction of ER stress after proteasome inhibition [4, 24, 25].

Bevacizumab. The incidence of HF related to bevacizumab-containing treatment is 2.2% in phase III studies. Uncontrolled hypertension and inhibition of VEGF signalling that impairs the adaptive response of the heart to pressure overload have been raised as potential mechanisms to explain this toxicity [26, 27].

Other kinases have been shown to present a role in survival or adaptation of cardiomyocytes to different injuries, and for
this reason the inhibition of these kinases could have a potential cardiotoxic role that should be taken into account in drug development. This group of kinases includes PDGFR, KIT, RAF and JAK2. PDGFR is expressed in cardiomyocytes and overexpression of PDGFR is known to induce cardiomyocyte survival [28, 10]. KIT has been shown to be necessary to recruit endothelial progenitor cells to injured areas in the heart. RAF1 has been shown to contribute in cardiac adaptation to pressure. JAK–STAT signalling seems to be protective in the heart at least maintaining cardiac capillary density, and its downregulation in mouse models increases the susceptibility to cardiac injury after myocardial ischaemia or anthracycline treatment [10].

**rhythm disturbances**

Paclitaxel can be considered as a prototypic pro-arrythmogenic cytotoxic drug. Paclitaxel has a chronotropic effect either directly on the Purkinje system or indirectly through histamine release mediated by its vehicle Cremophor EL that ultimately would lead to bradycardia [4].

The development of new drugs in the past decade has revealed a new spectrum of pro-arrythmogenic effects of anticancer drugs, the most important one consisting in QT interval prolongation [29, 30].

**QT interval prolongation**

QT interval is a measure of the total duration of ventricular activation and recovery (depolarization and repolarization). During depolarization the main event in cardiomyocytes is a sodium and calcium inflow that exceeds potassium outflow. When potassium outflow exceeds sodium and calcium inflow, repolarization occurs. In the electrocardiogram QT is measured from the beginning of the QRS complex to the end of the T wave. The QT interval is influenced by heart rate. There are several methods to correct QT for heart rate variation (Table 2). The definition of QTc prolongation varies in the literature, but most authors consider normal QTc ≤ 400 ms, and prolonged QTc > 450 ms in men and >470 ms in women. Ventricular arrhythmias, particularly torsades des pointes are correlated with QTc ≥ 550 ms, but there is no threshold below which prolongation QT interval is considered free of pro-arrhythmic risk [29, 30].

The most accepted hypothesis about the aetiology of QT prolongation is an interaction with HERG K channels. HERG K channels allow the rapid component of myocardial repolarization; when a drug interferes with their function, the potassium inflow decreases leading to prolongation of repolarization [29].

**Table 2. QT heart rate corrections**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazett</td>
<td>QTc = QT/RR¹/²</td>
</tr>
<tr>
<td>Fridericia</td>
<td>QT₀ = QT/RR¹/²</td>
</tr>
<tr>
<td>Framingham (Sagie)</td>
<td>QT₁ₑ = QT + 0.154 (1–RR)</td>
</tr>
<tr>
<td>Hodges</td>
<td>QTcH = QT + 105 (1/RR–1)</td>
</tr>
</tbody>
</table>

RR, interval from the onset of one QRS complex to the onset of the next QRS complex.

Of note, cancer patients may be prone to QT prolongation as many of them have electrolyte disturbances, take concomitant medications that could enlarge QT interval such as antiemetics, antifungals or antibiotics (Table 3), or have baseline electrocardiogram abnormalities (up to 32% of patients) (Table 4) [29, 30].

**arsenic trioxide.** The incidence of QT prolongation with arsenic trioxide treatment in clinical trials ranges from 26% to 93% [4].

**Table 3. Drugs producing prolonged QT interval**

<table>
<thead>
<tr>
<th>Category</th>
<th>Example Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, clomipramine, desipramine, imipramine</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Clarithromycin, erythromycin, spiramycin, pentamidine</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Ketoconazole, miconazole, itraconazole</td>
</tr>
<tr>
<td>Serotonin agonist/antagonist</td>
<td>Cisapride, ketaserin, zimeldine</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Phenothiazine, droperidol, haloperidol</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>IA: procainamide, quinidine, amaline, disopyramide</td>
</tr>
<tr>
<td></td>
<td>IB: flecain, propafenone</td>
</tr>
<tr>
<td></td>
<td>III: amiodarone, sotalol, dofetilide, ibutilide</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Bepridil, perhexiline</td>
</tr>
<tr>
<td>Other</td>
<td>Methadone</td>
</tr>
</tbody>
</table>

**Table 4. Risk factors for drug-induced QT interval prolongation and torsade des pointes**

<table>
<thead>
<tr>
<th>Category</th>
<th>Example Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Baseline ECG alteration</td>
<td>Baseline QT prolongation</td>
</tr>
<tr>
<td></td>
<td>Subclinical long QT syndrome</td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td>Myocardial ischaemia</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Cardiac hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Myocarditis</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Atrioventricular block</td>
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<tr>
<td></td>
<td>Hypokalaemia</td>
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<td></td>
<td>Hypomagnesaemia</td>
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<td></td>
<td>Hypocalcaemia</td>
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<tr>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Hyperaldosteronism</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>Subarachnoid haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>Intracranial trauma</td>
</tr>
<tr>
<td>Other diseases</td>
<td>Diabetes, cirrhosis</td>
</tr>
<tr>
<td>Related to drug administration</td>
<td>High drug concentration</td>
</tr>
<tr>
<td></td>
<td>Rapid rate of intravenous infusion</td>
</tr>
<tr>
<td></td>
<td>with a QT-prolonging drug</td>
</tr>
</tbody>
</table>

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In a multicentre study in acute promyelocytic leukaemia 40% of patients developed QT prolongation that returned to baseline 8 weeks after the end of treatment [31]. *Histone deacetylase inhibitors*. Histone deacetylase (HDAC) inhibitors target an epigenetic mechanism of acetylation that modulates transcription. Depsipeptide (FK228) is a cyclic peptide HDAC inhibitor. In a retrospective analysis of 500 patients who had received depsipeptide, five sudden deaths were reported. All these patients had risk factors for sudden death such as electrolyte abnormalities, concomitant therapy with a QTc-prolonging agent or hypertrophic cardiomyopathy. Documentation of increased QT was not obtained before sudden death. In other patients ST and T wave changes and QT prolongation were described as a class effect due to HDAC inhibition [29, 30, 32]. The incidence of QT prolongation associated with vorinostat, a phenylbutyrate-derived HDAC inhibitor, is 3.5%–6% [29].

*Scr/Abl kinase inhibitors*. QT prolongation was reported to occur in 2%–3% of patients treated with dasatinib, but <1% experienced a QTc interval of >500 ms [4]. *Multitargeted tyrosine kinase inhibitors*. Sunitinib has been shown to prolong the QT interval, the PR interval, causing bradycardia, and to induce ST and T wave changes [22]. Torsade de pointes has been observed in <0.1% of patients receiving sunitinib. The effect of sunitinib on QT interval is dose dependent [23].

Vandetanib is an oral selective inhibitor of VEGFR, epidermal growth factor receptor (EGFR) and RET tyrosine kinases. Preclinical studies showed an interaction of vandetanib with cardiac ion channels leading to repolarization abnormalities. In a phase I trial of vandetanib in solid tumours 9% of patients developed asymptomatic QTc prolongation, while in a Japanese phase I trial the incidence rose to 61% [29]. A study carried out in healthy volunteers showed that the effect on QT interval was increased by the combination of vandetanib with ondansetron. In phase II trials the incidence of asymptomatic QT prolongation was 15%, all events grade 1–2 [30].

Nilotinib, a multitargeted tyrosine kinase inhibitor against the Bcr–Abl fusion protein, KIT and PDGFR, has shown a mean QT prolongation in healthy volunteers of 18 ms [30]. In phase II trials the incidence of grade 2 QT prolongation has been 1%–4% [4]. In a phase I/II study five sudden deaths (0.6%) were reported considered probably or potentially related to nilotinib [34].

*Farnesyl protein transferase inhibitors*. Farnesyl protein transferase inhibitors selectively inhibit post-translational farnesylation of Ras and other proteins from other signalling pathways. In a phase II trial of lonafarnib (SCH66336) in patients with refractory head and neck squamous cell carcinoma 1 out of 15 patients developed grade 3 QTc prolongation and another patient presented syncope without previously documented QTc prolongation [29]. Asymptomatic QT prolongation was observed in two phase I trials with L-778123 and also in the phase I trial of the combination of L-778123 with paclitaxel [29].

*Vascular disruption agents*. Combretastatin A4 phosphate (CA4P) is a targeted natural tubulin inhibitor with a vascular disruption effect. In a phase I trial Dowlati et al. [35] described 7 cases of QTc prolongation out of 25 enrolled patients and two cases of cardiac ischaemia. In another phase I trial evaluating the combination of combretastatin with radiotherapy the QTc was increased by a mean of 13 ms, in all patients without related symptoms [36].

**protein kinase C inhibitors**

Enzastaurin is a protein kinase C inhibitor that suppresses the PI3K/Akt pathway, leading to anti-angiogenic effects, impairment of tumour growth and induction of tumour death. In a phase I trial 3 out of 47 enrolled patients developed asymptomatic grade 3 QTc prolongation. In the combination phase I trial of enzastaurin with gemcitabine one patient had a grade 2 QTc interval prolongation [29]. Finally, a phase II trial of enzastaurin 500 mg daily as second- or third-line treatment in patients with non-small-cell lung cancer showed 1 asymptomatic grade 1 QTc prolongation out of 55 patients [37].

*Hdm2 inhibitors*. Serdemetan, a novel inhibitor of the Hdm2–p53 complex, has shown prolongation of the QTc interval in the preliminary presentation of a phase I study [38].

**Ischaemia**

Several cancer treatments, including not only cytotoxic drugs but also radiotherapy and targeted therapies, are associated with an increased risk of coronary artery disease with or without coronary syndrome.

**Fluoropyrimidines**

5-Fluorouracil. The incidence of cardiotoxicity with 5-fluorouracil (5FU) in the literature varies from 1% to 68% [4] with a mean onset of 72 h after the initiation of administration. The most common cardiac symptom is angina-like chest pain, but some cases developed myocardial infarction (MI), arrhythmias, HF, cardiogenic shock and sudden death [4, 11]. Risk factors are not well defined but one of the most associated risk factors is a previous history of coronary artery disease. Other described risk factors are previous mediastinal radiotherapy and concomitant cisplatin therapy. The toxicity is described to be dose and rate dependent, as high doses (>800 mg/m²) and continuous infusion administration have been associated with higher rates of toxicity [4, 39].

Capecitabine. The incidence of cardiotoxicity related to capecitabine ranges from 3% to 9%. The onset of angina symptoms ranges from 3 h to 4 days after treatment has been initiated [4]. The main risk factor described is previous coronary artery disease.

**Pathophysiology**. The aetiology of fluoropyrimidine-related cardiotoxicity is still unknown. Several hypotheses have been raised including vasospasm PKC mediated, direct toxicity on the myocardium, coronary artery thrombus, activation of the coagulation system or autoimmune response [4, 11, 39]. The induction of vasospasm is the most likely mechanism as some studies have shown a contraction in the brachial artery or an increased level of endothelin-1 after 5FU infusion. In contrast, the co-administration of ergotamine to elicit vasospasm or the administration of vasodilating drugs as a preventive treatment has shown lack of benefit.
taxanes

Although the main cardiotoxicity of taxanes is bradycardia, ischaemia has also been described. The incidence reported with paclitaxel ranges from 0.5% to 5%, and with docetaxel is 1.7% [4]. The underlying mechanism of taxane-induced ischaemia is not well defined. It is also not known whether this is a direct effect of paclitaxel or is mediated by Cremophor EL vehicle through histamine release [4].

bevacizumab

In a pooled analysis of 1745 patients enrolled in five randomized trials in colorectal, non-small-cell lung cancer and metastatic breast cancer the incidence of angina and MI was 1.5% in the bevacizumab group [40]. In the observational BRiTE study in patients with colorectal cancer the incidence of MI was 0.6% [41]. Proposed risk factors include age >65 years and a previous history of arterial thrombotic event. These events can occur at any time during therapy but the median time to the event is 3 months. This toxicity does not seem to be dose related. A decrease in the regeneration process of endothelial cells after incidental trauma during anti-VEGF treatment has been proposed as a mechanism of development of arterial thrombotic events. This would allow the exposure of subendothelial collagen, which would activate tissue factor, increasing the risk of thrombotic events [43].

sorafenib

Sorafenib is a multi-kinase inhibitor that targets VEGFR2, VEGFR3, FLT3, KIT, PDGFR, RAF1 and BRAF. The incidence of myocardial ischaemia in clinical trials with sorafenib is ~3% [4, 10]. In considering the pathophysiology of cardiotoxicity induced by sorafenib the inhibition of VEGFR could have a similar role in maintenance of vascular integrity but also the inhibition of RAF activates two pro-apoptotic kinases, apoptosis signal-regulating kinase (ASK1) and mammalian sterile 20 kinase 2 (MST2), which have an important role in oxidant stress-induced injury in cardiomyocytes [10].

prevention and treatment

Several review articles have been recently published in order to clarify the underlying mechanism of anticancer drug cardiotoxicity and to improve the cardiologic follow-up of patients with cancer [1, 4, 30, 39, 44]. The appropriate management should include better detection of those patients at risk, the development of preventive strategies and the early treatment of cardiotoxicity when it does appear. We will highlight the main goals to achieve.

identification of the high-risk population

Schmidinger et al. [23] have shown that the pre-existing cardiac disease is underestimated in patients with cancer, as the incidence reported in the study was 9.3%. Many of the cardiovascular risk factors such as hypertension, diabetes, dyslipidemia or electrolyte disturbances can be treated and corrected before the anticancer treatment is started and thereafter closely monitored during therapy [1, 4, 30, 44]. Patients with pre-existing cardiac disease or taking drugs that potentially lead to QT prolongation should be evaluated by a cardiologist [30].

monitoring cardiac function

Despite the lack of consensus about the strategy to evaluate cardiotoxicity [44], periodic evaluation of LVEF should be carried out before, during and after treatment with cytotoxic or targeted agents known to induce HF in order to detect subclinical cardiac damage [1, 30].

For QTc monitoring, periodic electrocardiograms should be obtained, especially in patients at risk. A recommended schedule for cardiac monitoring could be to carry out a baseline ECG, another 7 days after initiation and periodically following any dose adjustments [30].

The development of better biomarkers to identify patients at high risk of cardiotoxicity [1] and the integration of different methods for cardiologic monitoring constitute a field of major research interest [44].

development of cardioprotective drugs

Most of the randomized trials with cardioprotective agents in patients receiving anthracyclines harbour methodological limitations. A meta-analysis of six randomized controlled trials with dexrazoxane, an ethylenediaminetetraacetic-acid-like iron chelator, showed a statistically significant benefit in favour of dexrazoxane for the occurrence of HF, without a difference in response rate or survival between the dexrazoxane and control groups [45]. The American Society for Clinical Oncology (ASCO) guidelines recommend that dexrazoxane treatment should be considered only in patients with metastatic breast cancer who have received a minimum of 300 mg/m² of anthracycline and would benefit from continued anthracycline-based therapy [46].

ACE inhibitors have been tested in a randomized trial in patients receiving high-dose chemotherapy with high serum troponin I levels. None of the 56 patients receiving the ACE inhibitor developed HF while 24% of the control patients developed it [47].

The identification of other endothelial or cardiomyocyte protective agents to prevent cardiotoxicity of anticancer drugs without decreasing their antitumoral effect continues to be a priority.

cardiotoxicity assessment in drug development

Following FDA and EMEA regulations, all phase I clinical trials have a rigorous cardiac monitoring plan. The identification of off-target toxic effects of kinase inhibitors and the development of new drugs that elicit those off-target kinases is also a goal. An example is the successful redesign of imatinib to reduce its cardiotoxic effects for the treatment of GIST [48].

early management of cardiotoxicity

Antineoplastic drug should be discontinued in the case of a cardiovascular event such as significant decrease in LVEF or the occurrence of a QTc prolongation of >500 ms [1, 30]. Other causes that could collaborate in this cardiovascular event, such as electrolyte disturbances or coronary disease, should be studied and treated.
In the case of LVEF dysfunction, early interventional treatment with ACE inhibitors and β-adrenergic blocking drugs has shown a clear benefit in adult patients with decreased LVEF not specifically caused by anthracycline therapy [4]. The benefit of ACE inhibitors in cancer patients has been studied in a single-centre study that proves that this treatment leads to LVEF recovery and also contributes to a reduction in cardiac events.

conclusion

Given the improvement in survival among cancer patients, prevention and treatment of cardiovascular diseases in this population of patients have gained relevance. A better knowledge about potential cardiac side-effects of antineoplastic drugs and the identification of patients at higher risk is a key strategy in reducing cardiotoxicity with these agents. Close monitoring is essential for an early detection and treatment of cardiovascular disease induced by antineoplastic treatment, and this policy minimizes serious acute and chronic cardiac consequences. The involvement of cardiologists during early clinical drug development will be instrumental in order to identify potential cardiac toxic effects in these patients and the best way to treat them from the onset.

disclosures

The authors have declared no conflict of interest.

references


