

review

## The cardiotoxicity of chemotherapy: New prospects for an old problem

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**Background.** Cardiotoxicity caused by chemotherapy, with its diverse early and late presentations, can hamper potentially curative or palliative treatments. The drugs most often linked to cardiotoxicity include anthracyclines, trastuzumab, 5-fluorouracil and taxanes, but some forms of cardiotoxicity have been described, more or less sporadically, for most antitumour agents. It is likely that the widespread use of the new biological target therapies will lead to the identification of other less known toxic effects. The available data on its incidence and clinical presentation, the pathogenetic mechanisms involved, the diagnosis, prevention and management of cardiac toxicity from chemotherapy are briefly reviewed.

**Conclusions.** The identification of novel molecular targets will increase the number of drugs available for the treatment of neoplastic disease. It will be important to evaluate the side effects related to treatment, particularly in organs with a limited regenerative capability such as the heart. Further studies will therefore be necessary.

Key words: antineoplastic agents – adverse effects – toxicity; heart – drug effects

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### Introduction

The available data on the incidence, risk factors, pathogenetic mechanisms involved, clinical presentation, diagnosis and management of cardiac toxicity from anti-

cancer drugs are briefly reviewed. The possibilities to intervene through alterations of the chemotherapy schedule or the use of cardioprotective agents are discussed. Not mentioned are the possible cardiac complications of radiotherapy and hormonal therapy.

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### Risk factors

Risk factors for the development of hypokinetic cardiopathy from anthracyclines include: elevated serum anthracycline con-

centrations following high doses and/or short infusions, previous or concomitant radiotherapy to the mediastinum or to the left hemithorax, age less than 15 years or over 65 years, cardiovascular risk factors such as arterial hypertension and diabetes, pre-existing hypokinetic cardiopathy and the female sex, in which morbidity and cardiac mortality are twice as frequent as in males in the presence of another cardiovascular risk factor.<sup>1-6</sup>

The only identified risk factors for trastuzumab are the type of chemotherapy pretreatment and the age of the patient that appear to be particularly influential in the group also treated with anthracyclines.<sup>7</sup> Regarding 5-fluorouracil, there is no consensus on age as a risk factor. Some authors report a more elevated risk in patients older than 50, while others do not.<sup>8-10</sup>

### **Anthracyclines**

The most frequently observed cardiotoxic effect after the use of anthracyclines (adriamycin or doxorubicin, daunorubicin, epirubicin and mitoxantrone) is the depression of myocardial contractility. About 10-15% of neoplastic patients treated with anthracyclines develop a hypokinetic cardiopathy<sup>11</sup>, and this depends mainly on the cumulative dose of the drug. The risk related to an adriamycin cumulative dose equal to 550 mg/m<sup>2</sup> is 7%; this grows linearly with higher dosages, reaching 50% for a total dose of 1000 mg/m<sup>2</sup>.<sup>1,12</sup> However, cardiotoxicity can also occur at a cumulative dose of less than 400 mg/m<sup>2</sup>, especially if the anthracycline is combined with other cytotoxic drugs, for example, cyclophosphamide.<sup>13</sup> Various hypotheses on the pathogenetic mechanisms of cardiopathy from anthracyclines have been formulated: the production of free radicals<sup>14</sup> and/or a reduction of free radical scavengers; the inhibition of the ionic

pumps through toxic metabolites<sup>15</sup>; alteration of the energetic mitochondrial metabolism<sup>16</sup>; the formation of a complex binding trivalent iron ions that damage cellular membranes and DNA<sup>3</sup>; the release of inflammatory cytokines<sup>11</sup>; and the induction of an adrenergic dysfunction.<sup>17</sup> Histological damage is characterized by the expansion of the sarcomere tubules and by the loss of actin and myosin myofilaments.

Cardiotoxicity can occur early or in a later phase. Acute toxicity, that is during chemotherapy infusion, occurs in 0.4 - 41% of cases<sup>11</sup>, especially in the presence of electrolytic alterations<sup>15</sup>, presenting mainly as sinus tachycardia, supraventricular or ventricular non-repetitive arrhythmia, aspecific alterations of repolarisation or an extension of the QT tract. In this phase, the patient is generally asymptomatic or only mildly so, and these alterations subside some hours after the discontinuation of the drug.<sup>1</sup> This type of cardiotoxicity is not a contraindication for further treatment with anthracyclines, but only after an adequate correction of the plasma electrolytes. However, cases of sudden death correlated to arrhythmia have been reported.<sup>2</sup>

Chronic toxicity appears weeks to months to years after the end of chemotherapy; it can also occur during treatment when the cumulative dose is elevated, or years after a first course of chemotherapy if the patient receives a second course. The incidence of chronic toxicity in anthracycline treated patients varies from 0.4 - 23%.<sup>18,19</sup> The appearance of signs and/or symptoms of congestive heart failure such as pulmonary edema or cardiogenic shock, which may occur progressively or unexpectedly, is frequent.<sup>12,13</sup> The ECG may be normal or may present ventricular conduction delays of different grades. Chest radiography may show possible signs of pulmonary congestion<sup>5</sup> with cardiac dimensions in the upper normal range. Echocardiography may

show hypokinesia, often more evident at the septal level, with a reduced function of the left ventricular pump which may or may not be associated with the involvement of the right ventricle, depending on the duration of the heart failure. The cardiac dimensions are frequently in the normal range or only slightly increased, but in the more serious cases or in the case of a late diagnosis, these may be greatly increased with evident remodeling. Parietal thickness is generally preserved. The diastolic mitralic flow may be normal or altered when seen on echodoppler. An endomyocardial biopsy may highlight vacuolisation of the cytoplasm and mitochondrial degeneration as well as the loss of myofibrils and perivascular fibrosis.<sup>20</sup>

The use of less cardiotoxic second generation anthracyclines such as idarubicin, epirubicin or mitoxantrone has been suggested and utilized in clinical practice. However, second generation anthracyclines are not devoid of cardiotoxicity, but generally at higher doses.<sup>18,21,22</sup> Moreover, the damage is cumulative even among different anthracyclines.

One strategy to limit doxorubicin cardiotoxicity is its encapsulation in liposomes which alters the tissue distribution and the pharmacokinetics of the drug, limiting its toxic effect on healthy tissue. The available data suggests a better cardiological safety profile of these formulations, both in monochemotherapy and in combination with trastuzumab or other cytotoxic agents.<sup>23,24</sup>

Attention to the cumulative dose and a careful cardiological follow-up still have the greatest role in the prevention of anthracycline cardiotoxicity. Measurement of the left ventricular pump function should be performed at baseline either by echocardiogram or by radionuclide angiography when a cumulative dose of 250-300 mg/m<sup>2</sup> of adriamycin or 500 mg/m<sup>2</sup> of epirubicin

or 25-30 mg/m<sup>2</sup> of mitoxantrone has been reached and repeated 10-30 days after the end of chemotherapy.<sup>14,25</sup> Late cardiotoxicity can be detected by extending the cardiological follow-up annually for at least 4-5 years after chemotherapy termination.

In the past, the prognosis of cardiomyopathy from anthracyclines was rather unfavourable. The two-year mortality rate of patients in the functional NYHA III-IV class, in treatment only with digitalis and diuretics, was 50%.<sup>26</sup> The prognosis in children appears to be better than that of adults<sup>1</sup>, with a two-year mortality rate of 20%.

After the introduction of the ACE-inhibitors for the treatment of patients with left ventricular dysfunction irrespective of the aetiology, the prognosis of patients with anthracycline cardiopathy clearly improved in terms of both morbidity and mortality. Moreover, the possible reversibility of left ventricular dysfunction has also been demonstrated.<sup>11,27,28,29</sup> The most used drugs are captopril and enalapril<sup>30</sup> at the same recommended dose as in other types of hypokinetic cardiopathy.

Currently, studies on the effectiveness of beta-blockers in this specific type of cardiopathy are less numerous.<sup>31,32</sup> However, small studies have shown a significant improvement of the left systolic ventricular function<sup>33,34</sup> and of the NYHA functional class<sup>35</sup> in patients with anthracycline cardiopathy receiving beta-blocker treatment. The principal drugs used in these patients are metoprolol<sup>33,35</sup> and carvedilol<sup>36</sup> at the doses recommended by the international guidelines for cardiac failure.

### **Trastuzumab**

Trastuzumab is a recombinant monoclonal antibody that targets the HER-2 receptor. It is effective in metastatic breast cancer

with a high HER-2 expression both as a single agent or in combination therapy and as first-line treatment or in pretreated patients. Being a very specific monoclonal antibody, it has a favourable toxicity/efficacy ratio. However, it can cause cardiotoxicity in the form of ventricular dysfunction and heart failure, especially if administered after or together with anthracyclines.<sup>7,37,38,39</sup> The mechanism of the toxicity is still not known, but some hypotheses have been formulated.

#### *Direct toxicity*

While HER-2 and HER-4 receptors are involved in cell growth, reparation and survival during the embryonic development of the heart, the normal adult muscle has few HER-2 receptors. Both HER-2 and HER-4 receptors have been detected in the myocardium of some cases showing clinical toxicity from trastuzumab.<sup>39,40</sup> In a small series of patients, the injection of radiomarked trastuzumab was followed by cardiac captation in about one third of the cases, and most of these presented subsequent cardiotoxicity.<sup>41</sup> Therefore, trastuzumab could have a direct cardiotoxic effect, at least in some subjects. Probably, there is an interpersonal variability in the expression of HER-2 and HER-4 receptors in the human myocardium as well as in the tumor itself.

#### *Indirect toxicity*

Cardiotoxicity is greater when trastuzumab is administered together with anthracyclines and, if this occurs under stress conditions, the HER-2 receptor is possibly involved in the reparative processes of damaged myocytes. This could suggest that the HER-2 receptor blockade prevents the myocardium from repairing the damage caused by anthracyclines, increasing their eventual toxic effect.<sup>39,42</sup>

Trastuzumab has an antitumoral specificity and a favourable toxicity/activity ra-

tio that will probably make it a more widely used agent in the next years. The recently available results on the impact of trastuzumab in the adjuvant therapy of breast carcinoma could be predictive of a more generalized use in patients with HER-2 hyperexpressing tumors after surgery. The evaluation of the cardiotoxicity will be of special importance in this context.

### **5-Fluorouracil**

In the literature, the frequency of fluorouracil-related cardiotoxicity such as angina, myocardial infarction, arrhythmia, heart failure and sudden death ranges from 1.6% -18%, with a mortality rate ranging from 2.2% to 13%. This variability is partly due to patient selection (inclusion or exclusion of those with pre-existing cardiopathy, especially of the ischemic type), to the study methods (retrospective or prospective; with provocative tests and/or close cardiological follow-up or limited to clinical observation only), to the method of drug administration (high or low doses; bolus or continuous infusion) and to the possible interference of other potentially cardiotoxic drugs in polychemotherapeutic regimens.<sup>8,9,43-47</sup> From a metanalysis of the literature, cardiotoxicity generally concerns 5-10% of unselected subjects receiving high doses (>800 mg/day), particularly in continuous infusion. In single bolus doses at 1-4 week intervals, as, for example, in the CMF regimen, it is generally well tolerated even in patients pre-treated with known cardiotoxic drugs such as anthracyclines.<sup>9,43-46,48</sup> This could be explained by the peculiar pharmacokinetics of fluorouracil, that has a brief plasmatic half-life of a few minutes only, but enters various tissues, including the myocardium, from which it is subsequently released in a variable number of days. In continuous

infusions, circadian variations of the haematic levels of the drug occur, partly due to fluctuations of the dihydropyrimidine-dehydrogenase (DPD) activity.<sup>49</sup> In most cases, the signs of cardiotoxicity appear 2-3 days after the beginning of treatment and they can also persist after the end of the infusion; therefore, only with very elevated doses of fluorouracil or in the case of continuous infusions can a high concentration of the drug in the cardiac tissue be sufficient to cause a toxic reaction.

The presence of ischemic cardiopathy or ECG alterations of an ischemic type may identify a group of patients with a more elevated risk of cardiotoxicity, but not all authors agree with this.<sup>8,9,10</sup> Hereditary congenital DPD defects can also cause significant fluorouracil toxicity, which is, however, mostly haematological.<sup>51</sup>

Generally, fluorouracil cardiotoxicity causes angina, with or without ECG signs of an acute heart attack or with ECG signs of ischemia in the absence of typical pain. Sudden death and arrhythmia, especially ventricular arrhythmia, follow in order of frequency. In several cases, ventricular arrhythmia and death have been described after the appearance of acute myocardial ischemia, while in other cases, sudden death occurred in the absence of cardiological follow-up and might have been due to a myocardial infarction. In conclusion, it can be hypothesized that in at least 90% of cases of toxicity, the primary cause is due to ischemia.<sup>28,47,51, 52</sup>

More rarely, toxicity appears in the form of cardiogenic shock, heart failure and a myocarditis type syndrome.<sup>47,51</sup> The majority of events appear during the first cycle of chemotherapy, and in more than half of the cases, within 72 hours from the beginning of the infusion, but in studies with a direct follow-up of the patients, the events occurred on the third or fourth day of a high dose continuous infusion.<sup>28,51,52</sup>

The ECG alterations consist either in the elevation or in the depression of the ST tract, diffuse or localized.<sup>33,34,40,41</sup> An onset with ST elevation leads to the supposition that vasospasm is the cause of the ischemia, as confirmed in some cases by angiographic documentation and experimental studies.<sup>53-56</sup> An interesting finding is the sporadically reported induction of vasospastic effort angina during the fluorouracil infusion. This event is probably underdiagnosed because of the generally scanty follow-up of outpatients.<sup>57</sup>

The mechanism of fluorouracil cardiotoxicity has not yet been entirely clarified, and could also be linked to different events which are more or less predominant in different patients. For example, the mechanisms underlying the induction of vasospasm are little known. Endothelin, that has been found to be particularly elevated in patients with tumors and fluorouracil toxicity, could possibly be a mediator, but it is also possible that other still unknown vasoactive compounds could be involved.<sup>57,58</sup>

In some cases of vasospastic effort angina, ischemia does not appear during stress but on recovery; therefore hyperventilation could play some role.<sup>52,59</sup> Other factors that could explain this phenomenon include the formation of thrombi, an increase in the oxygen requirement of myocytes from the inotropic and positive chronotropic effect, an interference with cellular metabolism, ATP depletion, inhibition of the tricarboxylic acid cycle, delayed immune reactions with lymphokine activation and cellular toxicity like that induced by anthracyclines.<sup>44,45,47,60</sup>

A specific therapy does not exist. The use of nitroderivatives, calcium channel blockers or a combination of these could be effective in the management or prevention of a recurrence of the toxicity in some patients; in others these measures could be completely or partially ineffective.

Arrhythmia and cardiogenic shock could be resistant to all conventional therapies or regress with a simple type of supportive therapy. As a rule, the discontinuation of fluorouracil leads to the regression of symptoms within 48-72 hours.<sup>9,28,43,51,52,54,61</sup> Once a patient has manifested cardiotoxicity, each further fluorouracil administration, even with the protection of antianginal drugs, carries an elevated risk of a repetition of the cardiotoxicity; therefore, a modification of the dose or of the method of administration can sometimes be effective.<sup>28,44,51</sup>

### Taxanes

Hypokinetic arrhythmia, particularly oligo- or asymptomatic sinus bradycardia but occasionally also transient atrioventricular II or III grade blocks, supraventricular and ventricular arrhythmia, depression of the systolic function and myocardial infarction have occurred in some studies involving paclitaxel, but in others no significant cardiotoxicity was reported.<sup>62-67</sup>

Some toxic effects, mainly arrhythmia, are analogous to those observed after accidental poisoning with parts of the yew plant and are probably due to paclitaxel itself. Others, particularly myocardial ischemia, ventricular arrhythmia and hypotension, may be due to the action of cremophore, the paclitaxel carrier, through the induction of histamine release, or to other substances used in the premedication.<sup>64</sup>

The combination of paclitaxel with doxorubicin causes an increased incidence of cardiotoxicity. It has been suggested that the interaction between the two agents, with delayed elimination of doxorubicin when administered after paclitaxel, is responsible for this effect.<sup>68</sup> Docetaxel, instead, does not seem to have cardiotoxic effects.

The mechanism of paclitaxel cardiotoxicity is strictly related to its antitumoral activity. In fact, the antimetabolic effect is due to its ability to stabilize the microtubules. At much higher doses than those effective in neoplastic cells, the same action occurs in the cardiac cells, affecting its elastic and electromechanical properties as seen in hypertrophy from fluid overload.<sup>67,69</sup> The effect would be a decrease of the spontaneous contraction frequency and a greater susceptibility to arrhythmia, without significant modifications of the contractility or muscle compliance; however, if the dose and time of exposure to paclitaxel is increased, a depression of contractility has been observed.<sup>67,69</sup>

It has also been suggested that the cardiotoxicity of taxanes is due to coronary vasoconstriction through a mechanism that is independent from the action on microtubules. This effect is observed only with paclitaxel and not with other analogues such as docetaxel, which has the same antimetabolic mechanism. The partial discrepancy of the data can perhaps be explained by the different methods of drug administration such as the dose, duration of the infusion and its association with other drugs. However, a general consensus seems to exist on the fact that the cardiotoxic effects of taxanes are transient and that the cellular dysfunction does not lead to necrosis as happens with anthracyclines; as a result, toxicity is not cumulative. Some toxic effects such as vasomotor phenomena, dyspnea and respiratory distress syndrome have an allergic origin, and are probably due to the drug carrier (Cremophor) or to the excipients rather than to the molecule itself; these symptoms generally respond to steroid treatment. It is, therefore, not necessary to submit all patients to a cardiological follow-up, but only those with bradyarrhythmia or conduction anomalies. The exclusion from taxane treatment of

all patients with a cardiological history is probably not justified.

### Other drugs

Effects like bradycardia, ventricular arrhythmia, heart failure, hypertension and myocardic ischemia have been ascribed to cisplatin and carboplatin. Some of these side effects have been described after polychemotherapies, generally in association with cyclophosphamide, vinca alkaloids, etoposide or fluorouracil, in which the role of platinum compounds is debatable. However, cisplatin can give haemodynamic and arrhythmic problems. The drug is nephrotoxic and therefore substantial amounts of hydration are given before and after its administration. In subjects with unstable cardiac compensation, hypertension or who have suboptimal compliance of the left ventricle, this could favour an acute pulmonary edema and/or a hypertensive crisis. The toxic effect on the kidney could explain other events such as ventricular arrhythmia, caused perhaps by hypomagnesemia and hypokalemia, a particularly frequent side effect, and hypertension.<sup>70-73</sup> In the more recent prospective studies in which the prevention of dysionia was prescribed, cardiac toxicity was not a problem. Moreover, carboplatin appears to be generally less toxic than cisplatin.<sup>74-76</sup>

Following gemcitabine therapy, arrhythmia, particularly atrial fibrillation, hypertension and heart failure have been described, but the role of gemcitabine as a cause of these phenomena is rather speculative.<sup>77,78</sup>

Cyclophosphamide can cause cardiotoxicity by damaging the capillary endothelium and also causing microthrombosis with subsequent hemorrhagic and ischaemic myocarditis, but this mainly concerns treatment with high doses of the drug.<sup>79</sup>

Important cardiotoxicity with arrhythmia and acute ischemic cardiopathy have been observed following cytokine treatment, in particular with intravenously administered interleukin-2 (IL-2) and  $\alpha$ -interferon. The cause seems to be mainly capillary leak syndrome in the case of IL-2 and a direct toxicity or vasculitis for interferon. Currently, following the subcutaneous administration of these drugs, their cardiotoxicity appears to be rare.<sup>80</sup>

Following the administration of vinorelbine, cases of myocardial infarction have been reported, and, when associated with trastuzumab, cases of depression of the pump function and of heart failure have been reported.<sup>81</sup> A more frequent problem is acute dyspnea, often associated with a hypertensive crisis and sometimes with thoracic pain generally related to bronchospasm or respiratory distress that disappears with the administration of oxygen, bronchodilators and cortisone. The ECG is usually normal.

Bleomycin does not have any particular cardiotoxicity, but is important with regard to the problems of differential diagnosis. This drug is an integral part of therapeutic regimens used in Hodgkin's lymphoma, head and neck cancer and testicular cancer. In the most favourable forms of Hodgkin's disease and testicular cancer, the percentage of cure is higher than 90%. The latter tumors are particularly frequent in young people with a long life expectancy in whom late toxicities are of paramount importance. The main dose-limiting effect of bleomycin is pulmonary toxicity (25-30% acute and 7-10% chronic).<sup>82-87</sup> Often, even long after treatment discontinuation, the patient may have to be referred to a cardiologist because of dyspnea. In these cases, the dose of anthracyclines and/or mediastinal radiotherapy need to be assessed, and a cardiological evaluation and respiratory function tests should be performed. The main risk

factors for bleomycin pneumopathy are age > 40 years, cumulative dose > 300 mg and concomitant radiotherapy to the lungs or platinum chemotherapy.

### Cardioprotective agents

A number of methods to reduce the risk of anthracycline cardiopathy have been suggested. The most widely used is the limitation of the cumulative dose of various drugs: 550 mg/m<sup>2</sup> for adriamycin, 600 mg/m<sup>2</sup> for daunorubicin, 1000 mg/m<sup>2</sup> for epirubicin, 1900 mg/m<sup>2</sup> for zorubicin and 160 mg/m<sup>2</sup> for mitoxantrone.<sup>3</sup> When an association with other antineoplastic cardiotoxic drugs or with radiotherapy to the mediastinum is scheduled, lesser doses should be used.

The administration of anthracyclines in smaller, more frequent doses and/or the prolongation of the time of infusion to 48-96 hours can reduce the cardiotoxic risk linked to elevated plasma concentrations of the drug. The use of less cardiotoxic derivatives of first-generation anthracyclines such as idarubicin, epirubicin or mitoxantrone has been suggested and performed in the clinical setting. However, second-generation anthracyclines can also cause cardiotoxicity, though at higher doses.<sup>18,21,22</sup> The damage is cumulative even between different anthracyclines.

Liposomes, used as adriamycin carriers<sup>23</sup> have been elaborated to lessen their toxic effect on healthy tissues; however, *in vivo* studies have not shown the same degree of cardiotoxicity prevention noted in *in vitro* studies. Besides, the elevated cost of the liposomal formulations limit their generalized use.

Many clinical studies have identified substances which are able to protect the myocardium from anthracycline toxicity without reducing their antineoplastic activity.<sup>88,89</sup> Cytoprotector agents such as

ICRF187 (dexrazoxane) at doses of 20:1 or 10:1 of the dose of adriamycin can reduce cardiac events to 30-50% and anthracycline cardiopathy to 10-15% of the original risk.<sup>90,91</sup> This intracellular iron chelator reduces the formation of free radicals<sup>92</sup> and promotes an immunomodulating effect on the myocardial inflammation caused by anthracyclines.<sup>93</sup> Although clinical studies have shown the effectiveness of this substance in preventing the initial cardiotoxicity from anthracyclines, there are no current randomized studies that have determined its role in the prophylaxis of myocardial damage in the long term.<sup>93</sup> Other studies have shown that dexrazoxane at high doses (>900 mg/m<sup>2</sup>) could have a counter effect on the antineoplastic activity of adriamycin and epirubicin<sup>94</sup>, including increasing the systemic clearance of the drug<sup>95,96</sup>; in addition, it can cause bone marrow toxicity and phlebitis at the administration site.<sup>93,97</sup> For these reasons, dexrazoxane is not used extensively in clinical practice, but mostly in patients with previous cardiac damage who have to receive further doses of anthracyclines. Other substances such as vitamin E, probucol, ascorbic acid, melatonin and other antioxidants have not yet shown an adequate *in vivo* cardioprotective effect.

Presently, the prevention of anthracycline cardiopathy is based on the cardiological follow-up of the patient. A knowledge of the possible cardiovascular risk factors, a sound clinical evaluation and the measurement of the left ventricular function before, during and after chemotherapy may lead to an early diagnosis of cardiotoxicity. In this case, the reduction or discontinuation of the drug and/or the beginning of an adequate cardioprotective therapy may improve and normalize the cardiac function. In this phase, the collaboration with the oncologist is of particular importance to clarify the risk/benefit ratio and to reduce, discontinue

or modify the cardiotoxic regimen.

Regarding trastuzumab, an *in vitro* study on human cardiomyocytes has shown a partial reversibility of the toxicity of the drug with the addition of recombinant neuregulines.<sup>41</sup> Periodic clinical and instrumental controls are advisable after 1-2 months and then every 6 months if there are no problems, more often if signs of toxicity are present. In the case of a left ventricular dysfunction, chemotherapy should immediately be discontinued and the usual medical therapy for heart failure begun, that is, diuretics, ACE-inhibitors, digitalis and beta-blockers when necessary, with a follow-up planned after a few weeks. The discontinuation of trastuzumab may result in a complete recovery of the cardiac function and the suspension of the cardiological therapy. In the event of trastuzumab cardiotoxicity, it should be permanently discontinued. Antidotes for cardiotoxicity are not yet available. It has also been suggested that the exposure to trastuzumab for a long time may induce apoptosis in neoplastic cells, but this mechanism has not yet been shown in the myocardium.<sup>98</sup>

Patients scheduled for therapy with fluorouracil should undergo an initial cardiological evaluation to rule out an ischemic cardiopathy. Patients with a higher risk should have a cardiological check-up 2-3 days after the start of the infusion if high doses are used (>800 mg/m<sup>2</sup>) or after two weeks in the event of chronic low doses, and, in the case of angina, a stress test should be performed. For patients with pre-existing ischaemic cardiopathy or with signs of cardiotoxicity from fluorouracil, the use of alternative drugs should be encouraged. When fluorouracil is essential, it should be administered in a protected environment with continuous ECG monitoring and the association of nitrates and calcium antagonists. A modification of the therapeutic scheme such as administering low

doses in weekly boluses rather than in continuous infusion could also be helpful.<sup>58,62</sup> When, despite these precautions, serious toxicity appears, fluorouracil should be no longer be administered.

### New agents

The cardiotoxic effects of some new anti-neoplastic agents are currently little known. As a matter of fact, the recent introduction of these drugs in clinical practice does not permit an adequate estimation of their cardiotoxic effects and further evaluation and investigation will be necessary. Examples of these drugs include monoclonal antibodies such as rituximab, a chimeric murine/human monoclonal antibody against the CD20 antigen on normal and malignant B-lymphocytes, bevacizumab, a monoclonal antibody that blocks vascular endothelial growth factor (VEGF) receptors, cetuximab, a chimeric antibody targeting the human epidermal growth factor (EGFR) receptor, and tyrosine kinase inhibitors such as imatinib, gefitinib and erlotinib and other classes of agents.

The identification of novel molecular targets will increase the number of drugs available for the treatment of neoplastic disease. It will be important to evaluate the side effects related to treatment, particularly in organs with a limited regenerative capability such as the heart. Further studies will therefore be necessary.

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