Review Article

"First, Do No Harm": Chemotherapy or Healthy Heart?

Apostolos K. Dimos, Pavlos N. Stougiannos, Athanasios G. Trikas

Department of Cardiology, "ELPIS" General Hospital, Athens, Greece

Key words:
Chemotherapy, cardiotoxicity, heart.

Manuscript received:
May 8, 2010;
Accepted:
September 24, 2010.

Address:
Athanasios G. Trikas

Department of Cardiology
"ELPIS" General Hospital
7 Dimitsanas St.
115 22 Athens, Greece
e-mail: atrikas@otenet.gr

The unthinking practice of medicine has been known to cause damage since the time of Hippocrates. Hence, the highest Hippocratic commandment to the physician was "First, do no harm." In modern clinical therapeutics, the evaluation of the real dimensions of the contribution of chemotherapy to cancer patients includes, apart from their positive actions, negative effects, too.

The balance between the hoped-for benefit and the expected toxicity is a daily concern in cancer patients, since no drug or therapeutic practice without toxicity exists outside the realm of ideas. Thus, for example, drugs that are administered for the relief of symptoms, i.e. to improve the quality of life, may quickly lead to the opposite, namely a deterioration in quality of life and unforeseen conditions.

The pathophysiology of toxicity has not been precisely elucidated and prediction is not always easy, since the same dose and the same way of administration may lead to different levels of toxicity. A large range of parameters may be involved in the actions and adverse effects of drugs; these include drug interactions, age (chronological and biological), general condition, organ function, the nature of the illness, as well as many genetic peculiarities of the individual patient, such as genes that code for enzymes that metabolise the drugs (Table 1).

Many cytostatic and cytotoxic drugs (Table 2) that are used in the treatment of various forms of cancer are associated with the occurrence of toxicity in normal tissues, such as the heart, which consist of cells that have limited regenerative capabilities. Although the goal of the newer drugs was to increase efficacy while reducing toxicity, this was unfortunately not feasible, even for those agents that were aimed at the special receptors and metabolic pathways of cancer cells and are not involved in the developmental and regenerative procedures of normal cells. Cardiotoxicity remains a serious problem, especially in cases where standard chemotherapy is combined with newer agents in order to achieve the maximum possible disease-free survival.[1]

Chemotherapeutic drugs and the heart

In the past, cardiotoxicity was considered to be a rare and relatively unimportant side effect of chemotherapy; however, in recent years that erroneous view has changed. For example, anthracycline (doxorubicin, DOX) can cause congestive heart failure or other cardiovascular events. Cardiac events may occur even at very small dosages, if the patient has risk factors, such as hypertension, arrhythmias, valvular diseases, coronary artery disease, metabolic disturbances, and advanced age, or has undergone chest radiotherapy for lymphoma or breast cancer.[2] It thus ap-

Table 1. Underlying aggravating factors.

Patient dependent:
• Pre-existing cardiovascular disease
• Risk factors for coronary artery disease
• Genetic substrate
• Pregnancy
• Exercise
Treatment dependent:
• Route of drug administration
• Drug dosage
• Time between chemotherapy sessions
• Combination of drugs and/or radiotherapy
• Survival time after chemotherapy

pears that the dose-dependent risk of cardiotoxicity is likely to be greater than is generally believed and the need for dose modification according to a patient's characteristics may possibly preclude achieving the maximum possible efficacy in that patient.

Another point that must be taken into consideration is the long-term performance of the cardiovascular system in patients who survive a tumour. In the USA at present there are 270,000 patients who have survived some form of childhood cancer and more than 10 million patients who have survived some form of cancer during their adult life.[3,4] A study from Scandinavia showed that these patients have a 5-year cardiac mortality of 5.9%.[5] Similar numbers were observed in the Childhood Cancer Survivor Study, during which children who had survived a cancer showed a fifteen-fold greater incidence of congestive heart failure, a tenfold greater incidence of cardiovascular diseases, and a 9-fold greater incidence of stroke, compared to controls.[3] Indeed, according to the investigators, the risk of occurrence of cardiovascular events was probably greater than that of a second tumour, especially in individuals who were treated with anthracycline or radiotherapy.[3] In addition, studies in asymptomatic children who survived a tumour showed that even low doses of DOX had a tendency to cause asymptomatic cardiac abnormalities that were revealed using non-invasive methods, while in a greater dosage it increased the risk of cardiac abnormalities by 4-5 times.[6] These observations are indicative that in children there is no absolutely "safe" dose of anthracyclines.[7] It appears that any exposure of children with cancer to anti-tumour drugs can cause cardiac abnormalities that may be clinically manifested under certain circumstances.[1] The same may also apply to adults who are treated with "safe" doses of chemotherapy.

However, for the time being, there is no evidence to support the avoidance of administration of chemotherapeutic agents in order to prevent cardiovascular complications; in fact, studies have shown that the benefit far outweighs the risk.[9] Nevertheless, their administration should be carried out with care and with regular monitoring of the patient, since there are also studies that arrived at more conservative results.[10] Furthermore, in some categories of patient, such as women with early breast cancer, targeted therapies should be preferred, instead of standard chemotherapeutic drugs. Targeted therapies do have moderate cardiotoxicity when administered as monotherapy, while they aggravate cardiotoxicity when coadministered with other chemotherapeutic agents.

The cardiotoxicity of targeted or combination therapies appears to be manageable or reversible during a short- or medium-term follow up, but there is the possibility of late cardiotoxicity.[11] For this reason, and because the expected survival is significantly longer in patients with early cancer, close monitoring of

Table 2. Chemotherapeutic drugs with cardiotoxic effects.

Antibiotics cytotoxic:	Antimetabolites:	Monoclonal antibodies:
Anthracyclines	5-fluorouracil	Trastuzumab
Doxorubicin	Capecitabine	Rituximab
Daunorubicin	Methotrexate	
Epirubicin	Fludarabine	Tyrosine kinase inhibitors:
Idarubicin	Cytarabine	Imatinib mesylate
Mitoxantrone		Sunitinib
Bleomycin		
Alkylating agents:	Anti-microtubule agents:	Miscellaneous:
Cyclophosphamide	Paclitaxel	Tretinoin
Ifosfamide	Docetaxel	Pentostatin
Cisplatin	Etoposide	Interferon
Mitomycin	Teniposide	Interleukin-2
Busulfan	Vinca alkaloids	

these patients is very important so that heart failure or any other cardiovascular complication may be diagnosed promptly. Congestive heart failure caused by anti-tumour drugs does not always respond to standard medication, especially when it is the result of the cumulative administration of anthracyclines. In some cases, heart transplantation may be the only indicated treatment for patients who have survived a tumour but have late, severe heart failure.[12]

Cardiotoxicity of chemotherapeutic agents

The clinical manifestations of chemotherapy-induced cardiotoxicity are many and various, according to the type of drug used and the existence or not of risk factors for cardiovascular diseases.

Anthracyclines

The problem of anthracycline cardiotoxicity has been known for 40 years. Safety limits have been determined, not only for DOX, but also for its analogues, such as epirubicin (EPI), daunorubicin (DNR), and idarubicin (IDA). It is believed that anthracyclines may become cardiotoxic after one- or two-electron reduction. One-electron reduction leads to the formation of free radicals that cause oxidative stress and a loss of energy from cardiomyocytes. Two-electron reduction results in a disturbance of calcium and iron homeostasis in the organism. Oxidative stress, the disturbance of calcium and iron ions, as well as the accompanying changes in the expressions of specialised cardiac genes, lead ultimately to the appearance of cardiomyopathy.[13] During recent years, our knowledge has increased concerning the pharmacokinetic and metabolic factors that determine the cardiotoxicity of anthracyclines. DOX and EPI can diffuse from cardiomyocytes into plasma, while other anthracyclines do not have this capability. Thus, their metabolites are concentrated in the heart and form reservoirs that stay there throughout a person's life. This probably explains why anthracyclines cause the appearance of late cardiotoxicity and why their cardiotoxicity increases when they are coadministered with other chemotherapeutic agents, which themselves have little or no effect on the heart.[14] The most characteristic example of synergistic toxicity is the combination of an anthracycline and a taxane, e.g. paclitaxel (PTX). Large studies have shown that the combination of DOX with PTX leads to cardiomyopathy and heart failure in about 19% of patients who take 420-480 mg DOX/m^2. This fact suggests that PTX accelerates anthracycline-induced cardiotoxicity. Similar results were observed from the administration of a PTX analogue, docetaxel (DCT).[15]

Taxanes

The taxanes PTX and DCT can have side effects on the cardiovascular system, primarily asymptomatic sinus bradycardia, which is seen in around 29% of patients.[16] The bradycardia may appear several hours after the start of the intravenous drug administration and disappears when medication is interrupted. Examination of myocardial cell cultures has shown that taxanes have a toxic effect, probably as a result of the action of taxanes on the microtubule network of the myocardial cells that interferes with their ability to replace sarcomeres. This is a disturbing finding, because it indicates that taxanes are toxic in themselves, independently of the coadministration of anthracyclines, especially under conditions of elevated myocardial stress. The toxicity of the combination of anthracyclines and taxanes can be reduced by decreasing the dose of DOX to 360 mg/m^2 and by administering one of the two drugs four days later.[17]

Other chemotherapeutic agents

Cardiotoxicity is a significant complication of other chemotherapeutic drugs, such as alkylating agents, antimetabolites, antibiotics, topoisomerase inhibitors, and tubulin-active agents.[18,19] These chemotherapeutic agents may cause cardiomyopathy similar to that of anthracyclines, ischaemia, myocarditis, and acute pericarditis. Typical examples are bleomycin, which may cause acute myocardial infarction either after the administration of a single dose or many years after the completion of treatment, and ifosfamide, which causes arrhythmias at low total doses or left ventricular dysfunction at high total doses.[20,21] Cardiotoxicity may also be caused by biological response modifiers (interferons,[22] interleukin-2), differentiating agents (trans-retinoic acid, arsenic trioxide), hormones (diethylstilbestrol, estramustine), and antihormones (aromatase inhibitors). It seems that the cardiotoxicity of the above chemotherapeutic agents, which do not belong to the anthracycline group, may be unpredictable and sometimes difficult to manage.

Targeted therapy

Cardiotoxicity has also been observed in targeted therapy, namely, with antibodies or low-mass inhibitors that target "tumour-specific" receptors. The HER2 receptor, which belongs to a wider group of growth factor receptors, is over-expressed in about 25% of patients with breast cancer. In the past, this expression was associated with aggressive disease and a bad prognosis. That has changed in recent years, with the use of trastuzumab (Herceptin), a monoclonal antibody that is administered for metastatic breast cancer and as adjuvant therapy in patients with operable breast cancer. In these patients the prognosis has improved significantly.[23] In healthy myocardium trastuzumab causes a reduction in systolic function that is independent of the dose administered, disappears on the cessation of medication, and does not reoccur on subsequent administration, while in rare cases endomyocardial biopsy reveals severe structural lesions.[24,25] The features of trastuzumab-induced cardiotoxicity (Type II) are different from that caused by anthracyclines (Type I). Although trastuzumab has a relatively "mild" effect on the myocardium, one study showed that the combination of trastuzumab, DOX and cyclophosphamide caused a severe degree of heart failure in 16% of patients. In contrast, the respective percentages were 4% for DOX and cyclophosphamide, 2% for trastuzumab and PTX, and 1% for trastuzumab alone.[26] This study clearly showed that trastuzumab, even in small doses, could exacerbate the cardiotoxicity of DOX. In addition, studies of the successive administration of anthracyclines and trastuzumab had equally disappointing results, with the incidence of severe or symptomatic heart failure remaining at high levels.[11] For this reason the US Food and Drug Administration recommended that coadministration of anthracyclines and trastuzumab should be avoided. Studies of trastuzumab so far have included only patients with normal cardiac function. Thus, the question arises as to the effect of the drug on the myocardium of patients with pre-existing heart disease or many cardiac risk factors. This is further complicated by our lack of knowledge of the long-term effects of trastuzumab on the myocardium. In addition, a recent study observed that the coexistence of a genetic polymorphism of HER2 significantly increases the risk of cardiac events, while not having any effect on the tumour or on long-term survival.[27]

Other agents used for the targeted treatment of tumours have also been implicated in unfavourable effects on the myocardium. Sunitinib and sorafenib are drugs that inhibit kinases, which promote the growth of cancer cells and neovascularisation, while bevacizumab is an anti-VEGF (vascular endothelial growth factor) agent.

Adverse effects of chemotherapy on the cardiovascular system

Table 3 shows the main clinical manifestations of cardiotoxicity from chemotherapeutic drugs.

Heart failure

The most characteristic side effect of chronic cardiotoxicity is asymptomatic systolic and/or diastolic left ventricular dysfunction, resulting in severe congestive cardiomyopathy that may eventually lead to death. Endocardial biopsy is the most sensitive and specific method of diagnosing and monitoring cardiotoxicity, but its invasive nature makes it difficult to apply on a regular basis.[28] For this reason, it is preferable to monitor left ventricular function using either echocardiography or radioisotope ventriculography, even though both these methods have a lower sensitivity than does biopsy. Diastolic dysfunction has been proposed as an index of early myocardial dysfunction.[29,30] However, for the time being there is insufficient evidence to prove that the systematic evaluation of diastolic function is useful in everyday clinical practice for a prompt and valid diagnosis of cardiotoxicity. Biochemical indexes, such as troponin I and T, can also assist in the early detection of cardiotoxicity, before the reduction in ejection fraction becomes apparent on the echocardiogram.[31] In particular, one study found that if troponin I levels showed a small increase during or after the end of chemotherapy, the patients might exhibit complications affecting the cardiovascular system,[32] whereas if troponin I levels remained low during chemotherapy and the following

Table 3. Clinical manifestations of cardiotoxicity caused by chemotherapeutic drugs.

Heart failure
Ischaemia
Hypotension
Hypertension
Oedema
Rhythm disturbances
Thromboembolic episodes
Myocarditis, pericarditis

few months, the patients had an excellent prognosis as regards myocardial function. However, long-term prospective studies will be needed to confirm these findings.

Another index for the assessment of myocardial function is B-type natriuretic peptide (BNP), a neurohormone whose levels increase in response to volume overload.[33] Studies of patients with tumours showed that high BNP levels are associated with impaired left ventricular function during treatment with anthracyclines.[34,35] In addition, BNP is elevated before the appearance of left ventricular dysfunction in patients who undergo therapy with high doses of chemotherapeutic drugs and bone marrow transplantation.[36]

Given that a decrease in myocardial function is a probable complication of chemotherapy, especially with anthracyclines, various techniques have been proposed to avoid it. Reducing the dose to less than 400 mg/m^2 and slowing the administration of the drug play an important role in limiting complications.[37] The liposomal forms of anthracyclines can further reduce their cardiotoxicity.[38,39] Dexrazoxane, which is a derivative of ethylenediaminetetraacetic acid (EDTA), can reduce the amount of free iron in myocytes and thus limit the formation of free radicals during the intravenous administration of anthracycline.[40] Dexrazoxane is generally used for the treatment of patients with metastatic breast cancer who have taken high doses of anthracycline (>300 mg/m^2), but it is not recommended from the start of therapy, because it can lessen the anti-tumour effect of anthracycline. In some studies, dexrazoxane showed a positive effect on survival, but whether this was the result of an improvement in cardiac function was not fully established.

Left ventricular dysfunction may be reversed with the interruption of therapy, management of risk factors for cardiovascular disease, and aggressive treatment of heart failure. Angiotensin-converting enzyme inhibitors and β-blockers are the most important drugs for heart failure. Their use in patients with a tumour and heart failure is essential; there are no contraindications and it is mandatory even in those who are under treatment with chemotherapeutic drugs. Indeed, cardiac function often deteriorates in patients with heart failure if this treatment is interrupted during chemotherapy. In patients with neoplasia, first-time heart failure is not always due to the chemotherapeutic agents. For this reason, it is essential to investigate other possible causes, such as ischaemia (Table 4).

Table 4. Incidence of heart failure in relation to chemotherapeutic agent.

Anthracyclines (6-10%)
Mitoxantrone (Novantrone) (1-5%)
Cyclophosphamide (Endoxan) (1-5%)
Mitomycin (Mutamycin) (1-5%)
Trastuzumab (Herceptin) (1-5%)
Alemtuzumab (Campath) (<1%)

Ischaemia

Retrosternal pain is another side effect that can appear in patients who are under chemotherapy. In these cases the chemotherapy is interrupted, an ECG is recorded, and cardiac enzymes are measured. If an acute coronary syndrome is identified, the patient should be treated in accordance with the guidelines of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology.[41,42] A low platelet count and cerebral metastases are a particular problem in certain patients with acute coronary syndromes, because anticoagulant therapy is contraindicated. These patients should be given aspirin and intensive anti-ischaemic medication with nitrates and β-blockers. Invasive management is also contraindicated in these patients, because heparin cannot be given. Platelet administration is not permitted, because platelets promote further thromboses. Many chemotherapeutic agents have been implicated in causing acute coronary syndromes. Intravenous administration of cisplatin can cause retrosternal pain, palpitations, and an elevation in cardiac enzymes.[43] Cisplatin is a special case among chemotherapeutic agents, because it can cause late hypertension, left ventricular hypertrophy, myocardial ischaemia and infarction, even 10 to 20 years after the remission of metastatic testicular cancer.[44] Furthermore, patients who have previously undergone chemotherapy or mediastinal radiotherapy are at increased risk of acute myocardial infarction after treatment with etoposide or other agents.[45,46] Other agents associated with acute coronary syndromes are 5-fluorouracil (5-FU),[47] capecitabine (Xeloda),[48] vinca alkaloids,[49] interferon-α, and bevacizumab (Table 5).[50,51]

Table 5. Incidence of ischaemic events in relation to chemotherapeutic agent.

Fluorouracil, 5-FU (1-5%)
Cisplatin (Platinol) (1-5%)
Capecitabine (Xeloda) (<1%)
Interleukin-2 (<1%)

Table 6. Incidence of hypotension in relation to chemotherapeutic agent.

Etoposide (Vepesid) (1-5%)
Alemtuzumab (Campath) (6-10%)
Cetuximab (Erbitux) (<1%)
Rituximab (MabThera) (1-5%)
Interleukin-2 (>10%)

Table 7. Incidence of hypertension in relation to chemotherapeutic agent.

Bevacizumab (Avastin) (1-5%)
Cisplatin (Platinol) (>10%)
Interferon-α (1-5%)

Hypotension

Hypotension is a commonly observed side effect of etoposide.[52] In addition, the administration of monoclonal antibodies may cause hypotension because of the massive release of cytokines. These agents may also cause fever, dyspnoea, or even death.[53,54] Alemtuzumab (Campath), an IgG antibody against CD52 antigen, has been associated with hypotension, bronchospasm, and rash from the first week of therapy. Cetuximab (Erbitux), a monoclonal antibody associated with the human epidermal growth factor receptor, may cause significant side effects, including hypotension, bronchospasm, and urticaria, in around 3% of patients.[55] Rituximab (Rituxan) a monoclonal antibody against the CD20 antigen, may cause side effects such as hypotension, angioedema, and bronchospasm within the first hours of administration.[56] For this reason, monitoring for hypotension is recommended in patients with known cardiovascular disease. Antihistamines, steroids, and slow infusion may be used to prevent as well as treat these side effects. Other measures include intravenous fluid administration, vasoconstrictive agents, bronchodilators and diphenhydramine (Table 6).

Hypertension

Bevacizumab can cause severe hypertension. In clinical studies, hypertension was observed in up to 5% of patients, with rarely reported cases of encephalopathy and subarachnoid haemorrhage. Hypertension may also be caused by interferon-α. Hypertension is treated by the administration of antihypertensive drugs (Table 7).[57]

Rhythm disturbances

Arsenic trioxide can cause ECG disturbances, with QT prolongation observed in >50% of the patients who take it. Other side effects are sinus tachycardia, non-specific ST-T changes, atrial fibrillation, and *torsades de pointes*. In addition, arsenic trioxide has been associated with the occurrence of complete atrioventricular block and sudden cardiac death.[58,59] For this reason, ECG monitoring is recommended for those patients who are taking arsenic trioxide, especially when coadministered with other agents that prolong the QT interval.

Thalidomide is relatively safe as regards cardiovascular disturbances and is generally well tolerated. The majority of its side effects can be managed by modifying the dose administered. However, thalidomide may cause severe sinus bradycardia.[60] The bradycardia is usually asymptomatic, but in patients who have concomitant conduction disturbances implantation of a permanent pacemaker may be necessary.

Finally, paclitaxel has been implicated in causing sinus bradycardia, atrioventricular block, ventricular extrasystoles, and ventricular tachycardia (Table 8).[61]

Oedema

Treatment with imatinib mesylate (Gleevec), a specific inhibitor of Bcr-Abl tyrosine kinase, has been associated with the occurrence of oedema, which may lead via significant fluid retention to pericardial or pleural effusion.[62] The presence of oedema is rarely life threatening and can often be fully treated with diuretics (Table 9).

Table 8. Incidence of rhythm disturbances in relation to chemotherapeutic agent.

Paclitaxel (Taxol) (<1%)
Thalidomide (Thalomid) (1-5%)
Arsenic trioxide (Trisenox) (>10%)

Table 9. Incidence of oedema in relation to chemotherapeutic agent.

Imatinib mesylate (Gleevec) (1-3%)
Thalidomide (Thalomid) (1-5%)

Table 10. Incidence of thromboembolic events in relation to chemotherapeutic agent.

Bevacizumab (Avastin) (5%)
Thalidomide (Thalomid) (5%)

Thromboembolic episodes

Bevacizumab administration has been associated with an increased risk of thromboembolic episodes, including stroke and myocardial infarction. The risk of fatal arterial thrombosis is also increased. Thrombi may be caused by administration of paclitaxel and thalidomide.[63,64] In patients with multiple myeloma the administration of low doses of coumarin is recommended for the prevention of possible deep venous thrombosis (Table 10).

Follow up of cancer patients by the clinical cardiologist in collaboration with the oncologist

So far, there are no guidelines concerning the definition, the diagnosis, and the therapy of cardiotoxicity from anti-tumour drugs. There is thus an urgent need for such guidelines. In the meantime, patients with cancer and cardiovascular diseases should be managed in accordance with the existing guidelines of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology for cardiac patients in general.

The prevention of cardiotoxicity begins before the start of cancer treatment, with a collaboration between the oncologist and the cardiologist. The former takes a complete history and evaluates the patient objectively as regards the treatment and/or prevention of cancer, while the latter evaluates haematological examinations, blood pressure, ECG, rhythm disturbances, and the echocardiogram, in order to assess cardiovascular function. In patients with a left ventricular ejection fraction <40%, heart failure, severe or unstable angina, a history of aortocoronary bypass, previous stroke, transient ischaemic attack or thromboembolic episodes, drug-refractory hypertension, or severe arrhythmias, special care must be taken throughout treatment because of the danger of adverse effects due to cardiotoxicity.

Thus, the cardiovascular profile must be taken into consideration by the oncologist when deciding on the therapeutic approach, with respect to the choice of drugs, the treatment timeframe, the drug dose administered in each session, the cumulative dose, and the route of administration. All are important factors that must be taken into account in order to avoid cardiotoxicity.

The clinical cardiologist and the oncologist clearly must work together so as to improve the prognosis of the disease and the overall patient survival (Table 11, Figure 1).[65]

Conclusions

The clinical manifestations of chemotherapy-induced cardiotoxicity are many and various, according to the type of drug used and the existence or not of risk factors for cardiovascular diseases. A better understanding of the side effects and full communication between cardiologists and oncologists will be of benefit,

Table 11. Cardiovascular monitoring of cancer patients. Reproduced from ref. 65, Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010; 102: 14-25, by permission of Oxford University Press.

Approach	Before antineoplastic therapy	During antineoplastic therapy and follow up
Clinical assessment	Familial and personal anamnesis	Physical examination; cancer therapy evaluation; risk reassessment
Tests	Blood pressure assessment; chest radiography; LVEF evaluation by any of these means: ECG, dynamic ECG, echo-Doppler, MUGA scanning	Blood pressure assessment; chest radiography; LVEF evaluation by any of these means: ECG, dynamic ECG, echo-Doppler, MUGA scanning
Serum markers	Troponin isoforms; B-type natriuretic peptide; myeloperoxidase	Troponin isoforms; B-type natriuretic peptide; myeloperoxidase
Prevention-Treatment	Lifestyle adjustments; ACE inhibitors; angiotensin II receptor blockers; β-blockers; prevention of thromboembolism with aspirin or anticoagulants or platelet antiaggregants	ACE inhibitors; angiotensin II receptor blockers; β-blockers; other appropriate therapies (i.e. anticoagulant therapies); change of antineoplastic therapeutic regimen (drug, schedule, or suspension)

ACE – angiotensin-converting enzyme; ECG – electrocardiogram; LVEF – left ventricular ejection fraction; MUGA – multiple gated acquisition.

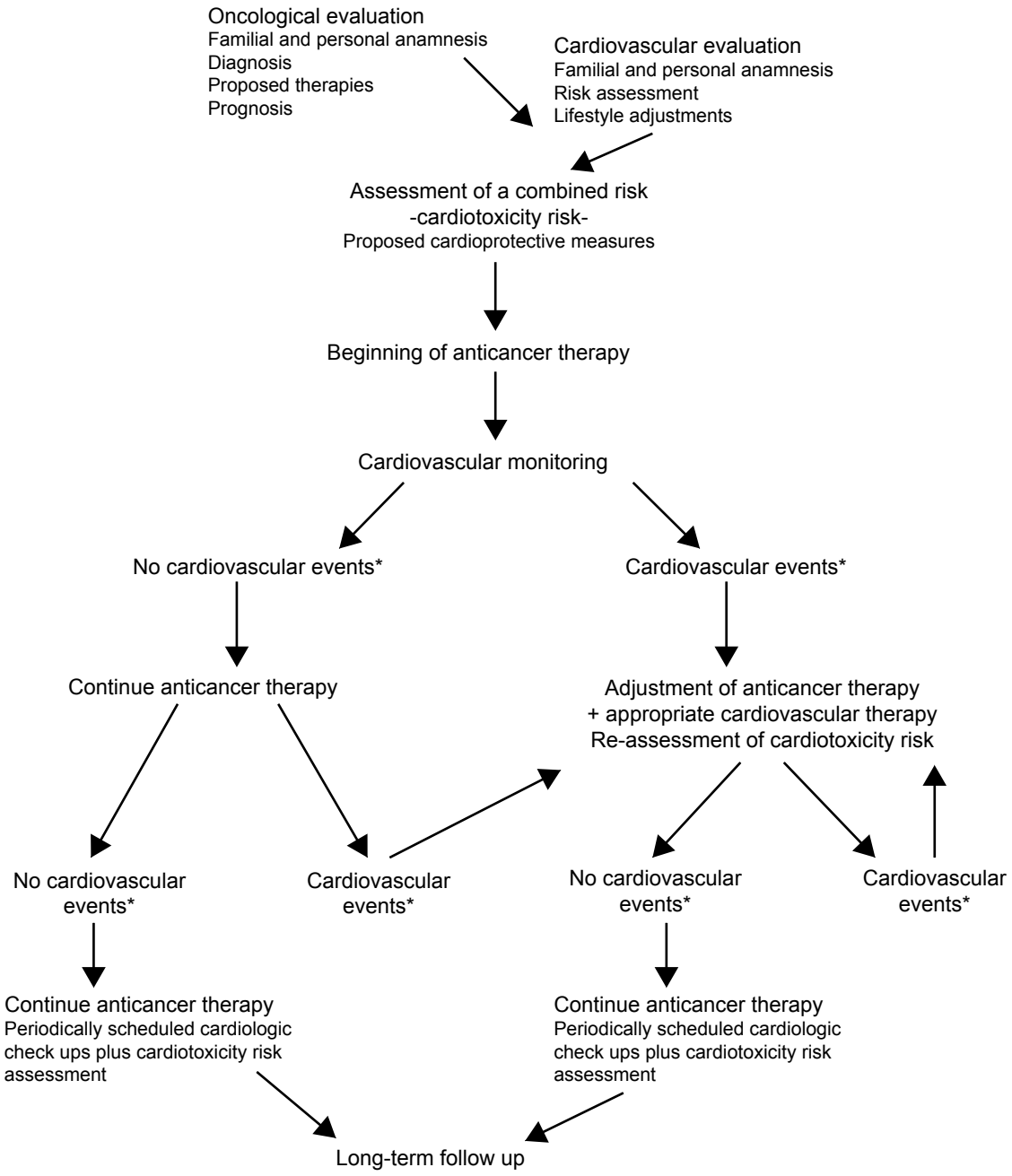

Figure 1. The oncologist and cardiologist should work together, evaluating the patient's cardiovascular risk level as an integral part of the choice of cancer therapy. In addition, the patient is monitored throughout therapy and follow up so that eventual cardiovascular alterations can be detected in a timely manner and treated either by intervention on the cardiovascular side or by modulation of the cancer therapy. Reproduced from ref. 65, Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010; 102: 14-25, by permission of Oxford University Press.

not only in terms of prompt risk prevention, but also for the best choice of anti-tumour therapy.

Thus, in the quest to foresee the response of the patient and the disease to medication, customised molecular and genetic medicine aims at the supreme goal of health care: "First, do no harm." The Hippocratic tradition has given us the tools to forge a path to new frontiers of clinical medicine.

References

1. Zuppinger C, Timolati F, Suter TM. Pathophysiology and diagnosis of cancer drug induced cardiomyopathy. Cardiovasc Toxicol. 2007; 7: 61-66.
2. Portera CC, Swain SM. The heart of the matter. J Clin Oncol. 2007; 25: 3794-3796.
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006; 355: 1572-1582.
4. Menna P, Salvatorelli E, Minotti G. Cardiotoxicity of antitumor drugs. Chem Res Toxicol. 2008; 21: 978-989.
5. Möller TR, Garwicz S, Barlow L, et al. Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: a population-based study in the Nordic countries. J Clin Oncol. 2001; 19: 3173-3181.
6. Hudson MM, Rai SN, Nunez C, et al. Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. J Clin Oncol. 2007; 25: 3635-3643.
7. Barry E, Alvarez JA, Scully RE, Miller TL, Lipshultz SE. Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. Expert Opin Pharmacother. 2007; 8: 1039-1058.
8. Limat S, Demesmay K, Voillat L, et al. Early cardiotoxicity of the CHOP regimen in aggressive non-Hodgkin's lymphoma. Ann Oncol. 2003; 14: 277-281.
9. Zambetti M, Moliterni A, Materazzo C, et al. Long-term cardiac sequelae in operable breast cancer patients given adjuvant chemotherapy with or without doxorubicin and breast irradiation. J Clin Oncol. 2001; 19: 37-43.
10. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol. 2007; 25: 3808-3815.
11. Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol. 2007; 25: 3525-3533.
12. Thomas X, Le QH, Fiere D. Anthracycline-related toxicity requiring cardiac transplantation in long-term disease-free survivors with acute promyelocytic leukemia. Ann Hematol. 2002; 81: 504-507.
13. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004; 56: 185-229.
14. Salvatorelli E, Menna P, Gianni L, Minotti G. Defective taxane stimulation of epirubicinol formation in the human heart: insight into the cardiac tolerability of epirubicin-taxane chemotherapies. J Pharmacol Exp Ther. 2007; 320: 790-800.
15. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005; 352: 2302-2313.
16. McGuire WP, Rowinsky EK, Rosenshein NB, et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med. 1989; 111: 273-279.
17. Perotti A, Cresta S, Grasselli G, Capri G, Minotti G, Gianni L. Cardiotoxic effects of anthracycline-taxane combinations. Expert Opin Drug Saf. 2003; 2: 59-71.
18. Schimmel KJ, Richel DJ, van den Brink RB, Guchelaar HJ. Cardiotoxicity of cytotoxic drugs. Cancer Treat Rev. 2004; 30: 181-191.
19. Floyd JD, Nguyen DT, Lobins RL, Bashir Q, Doll DC, Perry MC. Cardiotoxicity of cancer therapy. J Clin Oncol. 2005; 23: 7685-7696.
20. Ozben B, Kurt R, Oflaz H, et al. Acute anterior myocardial infarction after chemotherapy for testicular seminoma in a young patient. Clin Appl Thromb Hemost. 2007; 13: 439-442.
21. Quezado ZM, Wilson WH, Cunnion RE, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. Ann Intern Med. 1993; 118: 31-36.
22. Kontozis L, Soteriou M, Papamichael D, et al. Isolated right atrial metastasis of malignant melanoma mimicking a myxoma. Hellenic J Cardiol. 2011; 52: 281-284.
23. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. N Engl J Med. 2007; 357: 39-51.
24. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005; 23: 2900-2902.
25. Guarneri V, Lenihan DJ, Valero V, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. J Clin Oncol. 2006; 24: 4107-4115.
26. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001; 344: 783-792.
27. Beauclair S, Formento P, Fischel JL, et al. Role of the HER2 [Ile655Val] genetic polymorphism in tumorogenesis and in the risk of trastuzumab-related cardiotoxicity. Ann Oncol. 2007; 18: 1335-1341.
28. Mason JW, Bristow MR, Billingham ME, Daniels JR. Invasive and noninvasive methods of assessing adriamycin cardiotoxic effects in man: superiority of histopathologic assessment using endomyocardial biopsy. Cancer Treat Rep. 1978; 62: 857-864.
29. Marchandise B, Schroeder E, Bosly A, et al. Early detection of doxorubicin cardiotoxicity: interest of Doppler echocardiographic analysis of left ventricular filling dynamics. Am Heart J. 1989; 118: 92-98.
30. Ewer MS, Ali MK, Gibbs HR, et al. Cardiac diastolic function in pediatric patients receiving doxorubicin. Acta Oncol. 1994; 33: 645-649.
31. Lipshultz SE, Rifai N, Sallan SE, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation. 1997; 96: 2641-2648.
32. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004; 109: 2749-2754.
33. Maisel AS, Koon J, Krishnaswamy P, et al. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. Am Heart J. 2001; 141: 367-374.
34. Nousiainen T, Jantunen E, Vanninen E, Remes J, Vuolteenaho O, Hartikainen J. Natriuretic peptides as markers of cardiotoxicity during doxorubicin treatment for non-Hodgkin's lymphoma. Eur J Haematol. 1999; 62: 135-141.
35. Meinardi MT, van Veldhuisen DJ, Gietema JA, et al. Prospective evaluation of early cardiac damage induced by epirubicin-containing adjuvant chemotherapy and locoregional radiotherapy in breast cancer patients. J Clin Oncol. 2001; 19: 2746-2753.
36. Snowden JA, Hill GR, Hunt P, et al. Assessment of cardiotoxicity during haemopoietic stem cell transplantation with plasma brain natriuretic peptide. Bone Marrow Transplant.

2000; 26: 309-313.
37. Ewer MS, Ali MK, Mackay B, et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving Adriamycin. J Clin Oncol. 1984; 2: 112-117.
38. Gill PS, Espina BM, Muggia F, et al. Phase I/II clinical and pharmacokinetic evaluation of liposomal daunorubicin. J Clin Oncol. 1995; 13: 996-1003.
39. Muggia FM. Clinical efficacy and prospects for use of pegylated liposomal doxorubicin in the treatment of ovarian and breast cancers. Drugs. 1997; 54 Suppl 4: 22-29.
40. Von Hoff DD. Phase I trials of dexrazoxane and other potential applications for the agent. Semin Oncol. 1998; 25: 31-36.
41. Krumholz HM, Anderson JL, Bachelder BL, et al. ACC/AHA 2008 performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to develop performance measures for ST-elevation and non-ST-elevation myocardial infarction): developed in collaboration with the American Academy of Family Physicians and the American College of Emergency Physicians: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Society for Cardiovascular Angiography and Interventions, and Society of Hospital Medicine. Circulation. 2008; 118: 2596-2648.
42. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2008; 29: 2909-2945.
43. Berliner S, Rahima M, Sidi Y, et al. Acute coronary events following cisplatin-based chemotherapy. Cancer Invest. 1990; 8: 583-586.
44. Meinardi MT, Gietema JA, van der Graaf WT, et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. J Clin Oncol. 2000; 18: 1725-1732.
45. Schecter JP, Jones SE, Jackson RA. Myocardial infarction in a 27-year-old woman: possible complication of treatment with VP-16-213 (NSC-141540), mediastinal irradiation, or both. Cancer Chemother Rep. 1975; 59: 887-888.
46. Airey CL, Dodwell DJ, Joffe JK, Jones WG. Etoposide-related myocardial infarction. Clin Oncol (R Coll Radiol). 1995; 7: 135.
47. Gradishar WJ, Vokes EE. 5-Fluorouracil cardiotoxicity: a critical review. Ann Oncol. 1990; 1: 409-414.
48. Frickhofen N, Beck FJ, Jung B, Fuhr HG, Andrasch H, Sigmund M. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. Ann Oncol. 2002; 13: 797-801.
49. Yancey RS, Talpaz M. Vindesine-associated angina and ECG changes. Cancer Treat Rep. 1982; 66: 587-589.
50. Ackrill P, Ralston AJ, Day JP, Hodge KC. Successful removal of aluminium from patient with dialysis encephalopathy. Lancet. 1980; 2: 692-693.
51. Shah MA, Ilson D, Kelsen DP. Thromboembolic events in gastric cancer: high incidence in patients receiving irinotecan- and bevacizumab-based therapy. J Clin Oncol. 2005; 23: 2574-2576.
52. Cohen MH, Broder LE, Fossieck BE, Ihde DC, Minna JD. Phase II clinical trial of weekly administration of VP-16-213 in small cell bronchogenic carcinoma. Cancer Treat Rep. 1977; 61: 489-490.
53. Albanell J, Baselga J. Systemic therapy emergencies. Semin Oncol. 2000; 27: 347-361.
54. Mellstedt H. Monoclonal antibodies in human cancer. Drugs Today (Barc). 2003; 39 Suppl C: 1-16.
55. Saltz LB, Meropol NJ, Loehrer PJ, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol. 2004; 22: 1201-1208.
56. Cersosimo RJ. Monoclonal antibodies in the treatment of cancer, Part 2. Am J Health Syst Pharm. 2003; 60: 1631-1641.
57. Soignet SL. Clinical experience of arsenic trioxide in relapsed acute promyelocytic leukemia. Oncologist. 2001; 6 Suppl 2: 11-16.
58. Huang SY, Chang CS, Tang JL, et al. Acute and chronic arsenic poisoning associated with treatment of acute promyelocytic leukaemia. Br J Haematol. 1998; 103: 1092-1095.
59. Westervelt P, Brown RA, Adkins DR, et al. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. Blood. 2001; 98: 266-271.
60. Rajkumar SV, Gertz MA, Lacy MQ, et al. Thalidomide as initial therapy for early-stage myeloma. Leukemia. 2003; 17: 775-779.
61. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of taxol. J Clin Oncol. 1991; 9: 1704-1712.
62. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med. 2002; 346: 645-652.
63. Fanelli M, Sarmiento R, Gattuso D, et al. Thalidomide: a new anticancer drug? Expert Opin Investig Drugs. 2003; 12: 1211-1225.
64. Jekunen A, Heikkilä P, Maiche A, Pyrhönen S. Paclitaxel-induced myocardial damage detected by electron microscopy. Lancet. 1994; 343: 727-728.
65. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010; 102: 14-25.