clinical practice guidelines

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Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines

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introduction

New anticancer therapies have led to a long life expectancy for many patients; however, treatment-related comorbidities have become an issue for long-term cancer survivors. Cardiac toxicity is one of most feared side-effects of anticancer agents so that the gain in life expectancy due to anticancer therapy might be countered by increased mortality due to cardiac problems, above all heart failure (HF), but also myocardial ischaemia, arrhythmias, hypertension, thromboembolism.

Detection of cardiac injury is crucial since it may facilitate early therapeutic measures.

The incidence of cardiotoxicity depends on different factors related to oncological therapies (type of drug, dose administered during each cycle, cumulative dose, schedule of administration, route of administration, combination of other cardiotoxic drugs or association with radiotherapy) and to patient [age, presence of cardiovascular (CV) risk factors, previous cardiovascular disease (CVD), prior mediastinal radiation therapy]. Adverse cardiotoxic effects induced by chemotherapy are summarized in Table 1.

drugs associated with heart failure

anthracycline cardiotoxicity

The incidence of anthracycline-induced cardiotoxicity (AIC) varies depending on medication and cumulative dose: for doxorubicin from 4% to >36% in patient receiving 500–550 mg/m^2; epirubicin or idarubicin appears to have lower incidence of HF. However, it has been shown that the longer the follow-up, the higher the incidence of cardiac dysfunction.

AIC has been categorized as acute (transient decline in myocardial contractility immediately after infusion, incidence <1%), early onset chronic progressive (within first year after treatment, incidence 1.6%–2.1%), late onset chronic progressive, presenting as dilated cardiomyopathy (CMP) from at least 1 year after completion of therapy, until 10–30 years from the first dose of treatment. There are several hypotheses to explain the mechanism of AIC, but free radical formation is generally accepted as the main mechanism; apoptosis also has a prominent role in the myocardial cell loss that has been demonstrated in such cases. Risk factors for AIC, besides cumulative dose, are intravenous high single dose, time of drug infusion <30 min, history of prior irradiation, use of other concomitant agents such as cyclophosphamide, trastuzumab, paclitaxel, female gender, young or old age, underlying cardiovascular disease, increase in time elapsed since therapy administration. Among anthracyclines, liposomal doxorubicin showed reduced cardiotoxicity, albeit at the cost of hand–foot syndrome and sometimes other skin toxicity; thus it could be preferable in selected patients at high risk of HF.

Mitoxantrone, an antraquinone derivative, can cause cardiotoxicity that is similar to AIC: myocarditis and arrhythmias can be seen acutely with infusion, and after 1 year of monotherapy 3%–4% of patients have reduction in left ventricular ejection fraction (LVEF).

targeted drug cardiotoxicity

Targeted drugs are compounds acting through inhibition of specific target molecules: in the context of anticancer therapy, protein kinases, because of their critical role in cell signal transduction, are the most attractive targets.

In clinical practice there are two main classes of drug targeting tyrosine kinase receptors for growth factors: monoclonal antibodies (trastuzumab, bevacizumab) and small molecule tyrosine kinase inhibitors (TKIs: lapatinib, imatinib, sorafenib, sunitinib).

- Trastuzumab, a humanized monoclonal antibody that targets the extracellular portion of the human epidermal growth factor receptor 2 (HER2), is widely used in the treatment of HER2-positive breast cancer. The incidence of trastuzumab-related HF is 2%–7%; it increases with age >50 years, borderline LVEF before treatment, history of CVD and prior treatment with anthracycline and it rises to 27% when trastuzumab is used concurrently with anthracycline plus

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Table 1. Cardiovascular toxicity of chemotherapeutic agents

Drugs associated with CHF	Anthracyclines/ anthraquinolones
	Cyclophosphamide
	Trastuzumab and other monoclonal antibody-based tyrosine kinase inhibitors
Drugs associated with ischaemia or thromboembolism	Antimetabolites (fluorouracil, capecitabine)
	Antimicrotubule agents (paclitaxel, docetaxel)
	Cisplatin
	Thalidomide
Drugs associated with hypertension	Bevacizumab
	Cisplatin
	Sunitinib, sorafenib
Drugs associated with other toxic effects	
Tamponade and endomyocardial fibrosis	Busulfan
Haemorrhagic myocarditis (rare)	Cyclophosphamide (high-dose therapy)
Bradyarrhythmias	Paclitaxel
Raynaud's phenomenon	Vinblastine, bleomycin
Autonomic neuropathy	Vincristine
QT prolongation or torsades de pointes	Arsenic trioxide
Pulmonary fibrosis	Bleomycin, methotrexate, busulfan, high- dose cyclophoshamide

cyclophosphamide. Unlike AIC, trastuzumab toxicity is not dose related, and it is frequently reversible.

- Bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF) receptor, can be associated with HF or arterial thromboembolic events or venous thromboembolism, and it can induce severe hypertension.
- Lapatinib, a kinase inhibitor targeting internal HER2 and epidermal growth factor receptor, seems to have a low incidence of HF or other adverse cardiac effects.
- Imatinib, whose mechanism of cardiac injury is represented by mitochondrial dysfunction, has demonstrated deleterious effects on cardiomyocytes, in culture and *in vivo*; actually the precise rate of associated cardiotoxicity and its reversibility is still unknown and needs further investigation.
- Sunitinib and sorafenib, multitarget TKIs, have hypertension as the most common side-effect, but HF also is reported, especially in patients with a previous history of hypertension and coronary heart disease.

alkylating agent-correlated cardiotoxicity:

The incidence of HF reported with cyclophosphamide therapy ranges from 7% to 28%; the risk of cardiotoxicity is dose related (>150 mg/kg and 1.5 g/m^2/day), occurs normally within 10 days after administration of the first dose, and it is also correlated to prior anthracycline or mitoxantrone therapy or mediastinal irradiation.

drugs correlated with myocardial ischaemia/thromboembolism

The most commonly described cardiotoxic effect of fluorouracil (5-FU) is angina-like chest pain, with incidence ranging from 1% to 68% in the literature; cardiac events occur generally within 5 days after first administration, and ischaemic changes on ECG have been reported in 68% of patients; risk factors are high dose (>800 mg/m^2), continuous infusion of medicament, history of CVD, prior mediastinal radiation, concurrent use of chemotherapy; possible mechanisms of cardiotoxicity are coronary artery thrombosis, interaction with coagulation system, vasospasm, direct toxicity on myocardium.

- Paclitaxel can induce a large spectrum of cardiac disturbances of multifactorial aetiology, including ventricular arrhythmias, bradycardia, several degrees of atrioventricular conduction block, bundle branch block (effects caused by the paclitaxel vehicle Cremophor EL) and cardiac ischaemia, although these disturbances do not seem to result in serious sequelae in most patients; however, the clinical use of doxorubicin–paclitaxel combinations is limited by a higher incidence of the cardiac toxicity known to be induced by doxorubicin alone.
- Cisplatin has been shown to increase the risk of thrombotic events, such as deep vein thrombosis or pulmonary embolism, but specific cardiotoxicity is rarely reported.

monitoring of cardiotoxicity

cardiovascular evaluation of patients before treatment with anticancer agents

All patients undergoing chemotherapy should have prior careful clinic evaluation and assessment of CV risk factors or comorbidities [A].

Frequent vital signs monitoring is recommended during chemotherapeutic agent infusion, particularly with 5-FU or paclitaxel [A].

ECG and clinic cardiovascular evaluation are useful to screen signs of cardiomyopathy, conduction disturbances, QT interval, before beginning anticancer therapy with anthracycline or paclitaxel or small molecule TKIs [B].

With respect to imaging techniques, baseline Doppler echocardiogram (DEcho) is requested to assess cardiac function in patients undergoing therapy with anthracycline, particularly in the presence of CV risk factors, age >60 years, previous CVD, prior mediastinal irradiation [A]; baseline DEcho is needed to assess cardiac function in all patients undergoing therapy with trastuzumab, particularly in patients previously treated with anthracycline [A]. Left ventricular (LV) fractional shortening and ejection fraction (LVEF) are the most common indexes for cardiac function assessment before starting oncological therapy: LVEF <54% is identified as a risk factor for development of HF in patients undergoing treatment with trastuzumab. Multiple

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gated acquisition myocardial scintigraphy allows a very reliable assessment of LVEF, but its use is limited because of radiation exposure.

Magnetic resonance imaging (MRI), used to assess myocardial function, to evaluate myocardial perfusion and for tissue characterization, is not an ideal first-line screening test at present, but may have potential in the future.

With cardiac computed tomography (CT) up to today image quality is better than MRI but, because of considerable radiation dose, it is not considered a useful method to assess cardiac function.

monitoring during and after anticancer therapy

Endomyocardial biopsy represents the most reliable method for evaluation of myocardial damage but its very limited feasibility in daily clinical practice limits its use in cardiotoxicity monitoring.

Among the imaging techniques DEcho offers several advantages: it can assess LV systolic and diastolic dysfunction, heart valve disease, pericarditis and pericardial effusion, and carotid artery lesions. LV fractional shortening and LVEF are the most common indexes of LV systolic function for cardiac function assessment in oncology. LVEF is, however, not a very sensitive parameter in detecting early alterations in myocardial function. It is now recognized that the Doppler-derived diastolic indexes represent an early sign of LV dysfunction in cancer patients, so that evaluation of mitral diastolic flow pattern, early peak flow velocity to atrial peak flow velocity (E/A) ratio, deceleration time of E wave and isovolumic relaxation time can be useful to detect diastolic changes of LV function before systolic dysfunction occurs. Pulsed tissue Doppler may be easily performed during a standard Doppler echocardiographic examination; it has been successfully applied in several clinical setting and appears reliable in providing quantitative information on myocardial diastolic relaxation and systolic performance (E' wave, A' wave and S wave velocity). Tissue Doppler of LV lateral mitral annulus has a recognized prognostic role and, in combination with PW Doppler of mitral inflow, provides accurate information about the degree of LV filling pressure. Early changes in LV myocardial function of oncology patients were found by pulsed tissue Doppler of multiple LV sites.

B-type natriuretic peptide (BNP) is a cardiac hormone released by the myocardium in response to volume overload. An increase in BNP plasma level reflects an increased filling pressure of the LV as it occurs in LV dysfunction. Its value can rise when the HF is yet clinically unapparent and increases further according to HF severity. High levels of BNP correlate with LV dysfunction in cancer patients treated with oncological therapy. Nevertheless, further studies are requested to confirm the sensitivity and the specificity of this parameter.

Troponin is a specific and sensitive marker for detection of myocardial ischaemia, but elevation of troponin levels have been reported also after anthracycline therapy predicting subclinical and clinical cardiac morbidity and mortality; its use is limited because it needs numerous serial controls of serum levels at different time intervals.

recommendations for cardiotoxicity monitoring and management

Patients undergoing anticancer therapy should be encouraged to follow standard guidelines for reducing CV risk, such as blood pressure control, lipid level reduction, smoking cessation and lifestyle modifications.

- Periodic monitoring of cardiac function with DEcho is suggested especially for anthracyclines and their derivates, or monoclonal antibodies.
- Baseline clinical and ECG evaluation are recommended in all patients undergoing anthracycline therapy [III, A].
- Assessment of baseline systolic and diastolic cardiac function with DEcho should be conducted before treatment with monoclonal antibodies [III, A] or anthracyclines and their derivates in patients aged >60 years, or with cardiovascular risk factors such as hypertension, hypercholesterolaemia, diabetes, obesity or previous treatment with 5-hydroxytryptamine-2B agonists (in Parkinson or obese patients) potentially inducing cardiac valvulopathy, or documented cardiopathy or previous thoracic radiotherapy [III, A].
- Further evaluations of LVEF are recommended, even in asymptomatic patients, according to the follow timing: after administration of half the planned dose of anthracycline, or after administration of cumulative dose of doxorubicin 300 mg/m^2, epirubicin 450 mg/m^2 or mitoxantrone 60 mg/m^2 [III, A] or after administration of a cumulative dose of doxorubicin of 240 mg/m^2 or epirubicin 360 mg/m^2 in patients aging <15 years or >60 years [III, B]; before every next administration of anthracycline [III, A]; after 3, 6 and 12 months from the end of therapy with anthracycline [III, B].
- During the echocardiographic assessments, patterns of PW Doppler of LV inflow tract and TDI-PW Doppler of mitral anulus should also be evaluated to detect initial signs of LV dysfunction that might occur before reduction of LVEF.
- Periodic monitoring (every 12 weeks) of cardiac function is also suggested for those patients receiving monoclonal antibodies, especially if previously treated with anthracycline [III, A].
- Assessment of cardiac function is recommended 4 and 10 years after anthracycline therapy in patients who were treated at <15 years of age [III, B], or even at age >15 years but with cumulative dose of doxorubicin of >240 mg/m^2 or epirubicin >360 mg/m^2 [III, B].
- LVEF reduction of ≥20% from baseline despite normal function or LVEF decline <50% necessitate reassessment or discontinuation of therapy and further frequent clinical and echocardiographic checks.
- Aggressive medical treatment of those patients, even asymptomatic, who show LV dysfunction at DEcho after anthracycline therapy is mandatory, especially if the neoplasia could have a long-term survival; it consists of ACE inhibitors and β-blockers and the earlier HF therapy is begun (within 2 months from the end of anthracycline therapy), the better the therapeutic response
- A predictive role for biomarkers of cardiotoxicity caused by cancer therapy is not well defined enough to include them as

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routine screening measurements. Nevertheless, as persistent increases in cardiac troponin I or BNP concentrations seem to identify patients at risk of cardiotoxicity (except in the presence of the syndrome of inappropriate ADH secretion for the latter), a useful approach, even if rather costly and still controversial, is performing baseline assessment of biomarker concentrations and periodic measurements during therapy (at the end of chemotherapy administration, after 12, 24, 36, 72 h and 1 month later for troponin I; at the end of medicament infusion and after 72 h for BNP) to identify patients who need further cardiac assessment [III, C].

radiotherapy-related heart disease

A considerable amount of literature supports evidence of radiation-related heart injury after radiotherapy (RT) to the chest. The most appropriate groups of patients where radiation-associated cardiac injuries are of clinical importance are those with curable malignancies irradiated at a relatively younger age, so there is enough time to develop clinically significant late cardiac injury. Such malignancies are mainly Hodgkin's lymphoma and early-stage breast cancer, while there is an increasing number of lung and oesophageal cancer patients with long-term controlled disease who could develop post-RT cardiac sequelae.

Radiation-associated CV toxicity may be progressive. Complex, combined disease of heart coronary arteries, valves, myocardium and conduction system as well as diastolic dysfunction may be seen. Estimates of relative risk of fatal CV events after mediastinal irradiation for Hodgkin's disease ranges between 2 and 7 and after irradiation for left-sided breast cancer from 1.0 to 2.2.

Risk factors for radiation-associated heart damage include: dose >30–35 Gy, dose per fraction >2 Gy, large volume of irradiated heart, younger age at exposure, longer time since exposure, use of cytotoxic chemotherapy, endocrine therapy or trastuzumab, presence of other risk factors such as diabetes, hypertension, dyslipidaemias, obesity, smoking, etc.

evidence from breast cancer patients

In the last update of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis on locoregional RT, comparison of CV mortality between patients treated with and without RT has shown a statistically significant relative risk of 1.27. A similar latent time was estimated in an overview of trials started before 1975.

In a Swedish study that included 55 000 patients a mortality ratio of all CV disease for left versus right side in a period of >10 years after treatment was 1.10 [95% confidence interval (CI) 1.03–1.18] for all CV diseases and 1.13 (95% CI 1.03–1.25) for deaths from ischaemic disease. Other studies confirm those results.

evidence from Hodgkin's lymphoma patients

Mediastinal radiotherapy can cause a variety of CV complications such as pericarditis, myocardial fibrosis, coronary artery disease, valvular abnormalities and conduction disturbances. Restrictive cardiomyopathy, valvular defects and conduction defects, persistent tachycardia and blunted haemodynamic responses to exercise are usually diagnosed. Nevertheless myocardial infarction is the major cause of higher long-term mortality in survivors of Hodgkin's disease.

It is very important to note that death due to cardiac causes is estimated to be responsible for about one-quarter of the mortality from reasons other than Hodgkin's disease itself, which equals 2%–5% of overall mortality in those with Hodgkin's disease.

cardiac structures affected by radiation

Injury of the various structures and tissues in the heart can cause a spectrum of radiation-induced CV diseases.

- Arteritis of the endothelium of coronary arteries can cause premature coronary artery disease and atherosclerosis mainly in left anterior descending and right coronary artery. Time of appearance is 10–15 years after RT.
- Acute pericarditis and symptomatic (haemodynamic compromise with constriction or tamponade) or asymptomatic chronic pericardial effusion, appears usually 6–12 months following RT.
- Myocarditis and congestive heart failure due to non-specific diffuse interstitial fibrosis.
- Valvular stenosis and regurgitation mainly of mitral and aortic valves.
- Fibrosis of the conduction system and disturbed heart rate and complete or incomplete heart block.
- Some indirect implications on the heart may result from irradiation of adjacent structures. Lung and mediastinal fibrosis may result in respiratory insufficiency, pneumonic hypertension and may complicate any potential heart surgery. Hypothyroidism may affect the lipid profile and CV function. Mediastinal venous and lymph vessel obstruction may cause pericardial effusion or chylothorax.

Radiation tolerance doses for the above late-effects have been estimated to be between 30 and 40 Gy.

recommendations to reduce cardiac toxicity in patients treated by radiotherapy

There is some evidence that newer irradiation techniques seem to decrease the risk of RT-induced cardiac disease, but a longer follow-up time is needed to confirm it. Modern RT techniques include three-dimensional treatment planning with DVH (dose volume histogram) for accurate heart volume and dose calculation. Linear accelerator photons and multiple-field conformal or intensity-modulated radiotherapy (IMRT) are desirable for chest irradiation.

For (left) breast/chest wall RT, 6 MV or occasionally higher energy photons (for large breasts) from a linear accelerator should be used.

The introduction of cardiac-sparing lead block during standard simulator planning will result in cardiac irradiation being at least partially avoided in many patients. The use of

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a four-field IMRT technique can offer better sparing than the partial shielding technique as the maximum heart depth is increased. The IMRT plans also showed improved dose homogeneity within the PTV but may be associated with increased irradiation of the contralateral breast.

It has been proposed that maximum heart distance (MHD) i.e. the maximal distance between anterior cardiac contour and posterior tangential field edges as seen on beam's eye view is a reliable predictor of the mean heart dose in left-tangential breast or chest wall irradiation, and may be useful in centres where three-dimensional cardiac dose assessment is not routinely available. A strong linear correlation was found between the MHD and the mean heart dose: for every 1-cm increase in MHD, the mean heart dose increased by 2.9% on average (95% CI 2.5–3.3).

Electron beams can be used for the treatment of superficial structures such as in the internal mammary lymph nodes or the boost dose on the breast after tumorectomy, in the treatment of breast cancer.

For mediastinal RT, high-energy photons from a linear accelerator should be used to treat patients with equal weighting of anterior and posterior portals (instead of anterior weighting), all fields should be treated on each RT fraction, use of a subcarinal block after a dose of 30 Gy, and use of shrinking-field technique are the most important parameters to minimize heart exposure. As Adams et al. has stated, although permanent complications tend to occur less frequently under a total dose of 40 Gy, it is not a good idea to systematically limit treatment, which may be inadequate to control the neoplastic disease.

treatment of radiotherapy-related heart complications

Radiation-induced heart diseases are treated as non-radiation-related ones, but with special attention to the changes radiation causes to the heart and other structures of the chest.

monitoring of cardiac function after chest radiotherapy

Patients at high risk for radiotherapy-induced complications are those treated as children or young adults for Hodgkin's lymphomas with a mediastinal/heart dose of >30 Gy, mainly with what it are called outdated RT techniques (see above). Those patients should be informed and followed up closely [III, A]. Radiation-related heart toxicity is extremely rare during RT.

Breast cancer patients treated by cytotoxic chemotherapy or monoclonal antibodies should be monitored. Patients treated by postoperative breast RT (with or without adjuvant endocrine treatment) are not regularly monitored for cardiac problems although RT should be considered as a risk factor when heart disease is diagnosed in those patients [III, B].

Data to support definitive recommendations on various tests and their frequency do not exist. However, RT-induced risk is lifelong and requires long-term follow-up. Screening and monitoring of heart function is identical to the standard tests and procedures cardiologists use for other patients, and consequently the follow-up protocols are based on departmental or personal experience and on each patient's needs and clinical picture. There is therefore a need for both oncologists and cardiologists to be aware of the risks and underlying pathophysiology of RT-related heart complications.

Apart from clinical examination and medical history, tests usually requested depend on the studied abnormality.

- Coronary artery disease: lipid profile, exercise stress test, radionuclide, angiography, echocardiogram, ECG.
- Pericarditis: electrocardiogram (ECG), chest X-ray and echocardiogram.
- Cardiomyopathy: electrocardiogram, echocardiogram, radioisotopic angiography.
- Arrythmias: ECG and 24-h RCG.
- Valvular disease: echocardiogram, cardiac catheterization.

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