Atrial Fibrillation

Anticoagulation options include therapeutic low-molecular-weight heparin (LMWH) (as a short- to intermediate-term measure), a vitamin K antagonist (e.g. warfarin) if international normalized ratio control is stable and effective, or a non-VKA oral anticoagulant (NOAC).

Strategies to reduce chemotherapy-induced cardiotoxicity

Before cardiotoxic anticancer treatment

<table>
<thead>
<tr>
<th>Chemotherapy drug</th>
<th>Potential cardioprotective measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>All chemotherapy drugs</td>
<td>Identify and treat cardiovascular risk factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anthracyclines and analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limit cumulative dose (mg/m²):</td>
</tr>
<tr>
<td>- Daunorubicin ≤800</td>
</tr>
<tr>
<td>- Doxorubicin ≤360</td>
</tr>
<tr>
<td>- Epirubicin ≤720</td>
</tr>
<tr>
<td>- Mitoxantrone ≤160</td>
</tr>
<tr>
<td>- Idarubicin ≤150</td>
</tr>
</tbody>
</table>

Altered delivery systems (liposomal doxorubicin) or continuous infusions

Doxorubacine as an alternative

ACE-Is or ARBs

β-blockers

Statins

Aerobic exercise

Trastuzumab

ACE-I

β-blockers

ACE = angiotensin converting enzyme; ACE-I = angiotensin converting enzyme inhibitor; CAD = coronary artery disease; HF = heart failure; HTN = hypertension; PAD = peripheral artery disease.

Thromboembolic disease

Clinical factors associated with increased risk of cancer-associated venous thromboembolism (modified from Khorana et al.)

Cancer-related factors
- Primary site of cancer (mostly pancreas, brain, stomach, kidney, lung, lymphoma, myeloma)
- Histology (especially adenocarcinoma)
- Advanced stage (metastatic)
- Initial period after cancer diagnosis

Patient-related factors
- Demographics: older age, female sex, African ethnicity
- Comorbidities (infection, chronic kidney disease, pulmonary disease, atherosclerotic disease, obesity)
- History of venous thromboembolism, inherited thrombophilia
- Low performance status

Treatment-related factors
- Major surgery
- Hospitalization
- Chemotherapy and anti-angiogenic agents
- Hormonal therapy
- Transfusions
- Central venous catheters

Anticoagulation options include therapeutic low-molecular-weight heparin (LMWH) (as a short- to intermediate-term measure), a vitamin K antagonist (e.g. warfarin) if international normalized ratio control is stable and effective, or a non-VKA oral anticoagulant (NOAC).
Myocardial dysfunction and heart failure

Left ventricular (LV) dysfunction and heart failure (HF) are relatively common and serious side-effects of anticancer treatments.

Baseline risk factors for cardiotoxicity

**Current myocardial disease**

- Heart failure (with either preserved or reduced ejection fraction)
- Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide)
- Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia)
- Moderate and severe VHD with LVH or LV impairment
- Hypertensive heart disease with LV hypertrophy
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Restrictive cardiomyopathy
- Cardiac sarcoidosis with myocardial involvement
- Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)

**Demographic and other CV risk factors**

- Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for adriamycin)
- Family history of premature CV disease (<50 years)
- Arterial hypertension
- Diabetes mellitus
- Hypercholesterolaemia
- Smoker
- High alcohol intake
- Obesity
- Sedentary habit

**Previous cardiotoxic cancer treatment**

- Prior anthracycline use
- Prior radiotherapy to chest or mediastinum

**Lifestyle risk factors**

- Smoking
- High alcohol intake
- Obesity
- Sedentary habit

---

**Key points**

- Cancer patients treated with a potentially cardiotoxic therapy are at high risk of developing HF and should therefore receive medical care aimed at obtaining a strict control of cardiovascular risk factors.
- Left ventricular ejection fraction (LVEF) should be determined before and periodically during cardiotoxic treatment for early detection of cardiac dysfunction.
- This group has decided to consider the lower limit of normal of LVEF in echocardiography as 50%, in line with the definition of cardiotoxicity commonly used in registries and trials in patients with cancer.
- A patient with a significant decrease in LVEF (e.g. a decrease >10%), to a value that does not drop below the lower limit of normal, should undergo repeated assessment of LVEF shortly after and during the duration of anticancer treatment.
- If LVEF decreases >10% to a value below the lower limit of normal (considered as an LVEF <50%), angiotensin converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers (ARBs)) in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated, as these patients are at high-risk of developing HF.
- ACE-inhibitors (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated.

**Coronary artery disease**

Myocardial ischaemia, infarction and ischaemia-induced arrhythmias, are side-effects of several anticancer therapies.

- Assessment of CAD should be based on the history, age and gender of the patient, considering the use of chemotherapy drugs as a risk factor for CAD.
- Clinical evaluation and, when necessary, testing for detection of myocardial ischemia is key to identify patients with latent pre-existing CAD. This may have implications in the selection of cancer treatment.
- Patients treated with pyrimidine analogues should be closely monitored for myocardial ischaemia using regular ECGs, and chemotherapy should be withheld if myocardial ischaemia occurs.
- Drug rechallenge after coronary vasospasm should be reserved when no other alternatives exist, and only under prophylaxis and close monitoring of the patient. Pretreatment with nitrates and/or calcium channel blockers may be considered in this setting.
- Long-term clinical follow-up and, when required, testing for presence of coronary artery disease (CAD), may be useful to identify patients with cardiac disease who develop long-term complications of chemotherapy and radiotherapy.

---

**Arrhythmias**

**Cancer drug agents associated with cardiac arrhythmias**

<table>
<thead>
<tr>
<th>Type of arrhythmia</th>
<th>Caustive drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>Arsenic trioxide, bortezomib, cepabactine, cisplatin, cyclophosphamide, doxorubicin, epirubicin, 5-FU, fltostamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>Anthracyclines, carmustine.</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>Anthracyclines, arsentic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.</td>
</tr>
<tr>
<td>Conduction disturbances</td>
<td>Anthracyclines, cisplatin, 5-FU, imatinib, taxanes.</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Alkylating agents (cisplatin, cyclophosphamide, fltostamide, melphalan), anthracyclines, antimetabolites (cepabactine, 5-FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponstatin, sorafenib, sunitinib, irbitumab), topoisomerase II inhibitors (amascrine, etoposide), taxanes, vinca alkaloids.</td>
</tr>
<tr>
<td>Supraventricular tachycardias</td>
<td>Alkylating agents (cisplatin, cyclophosphamide, fltostamide, melphalan), amascrine, anthracyclines, antimetabolites (cepabactine, 5-FU, methotrexate, bortezomib, doxorubicin, IL-2, interferons, pacltazel, ponstatin, romidepsin.</td>
</tr>
<tr>
<td>Ventricular tachycardia/fibrillation</td>
<td>Alkylating agents (cisplatin, cyclophosphamide, fltostamide, melphalan), amascrine, antimetabolites (cepabactine, 5-FU, gemcitabine), arsentic trioxide, doxorubicin, interferons, IL-2, methotrexate, paclitaxel, proteasome inhibitors (bortezomib, carbiotomib), rituximab, romidepsin.</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>Anthracyclines (reported as very rare), arsentic trioxide (secondary to torsade de pointes), 5-FU (probably related to ischaemia and coronary spasm), interferons, nicotin, romidepsin.</td>
</tr>
</tbody>
</table>

**QT prolongation**

- A 12-lead ECG should be recorded and the QT interval, corrected for heart rate with Bazett’s or Fridericia’s formula, should be obtained in all patients at baseline.
- Patients with a history of QT prolongation, relevant cardiac disease, treated with QT-prolonging drugs, with bradycardia, thyroid dysfunction, or electrolyte abnormalities should be monitored by repeated 12-lead ECG.
- Consider treatment discontinuation or alternative regimens if the QTc is >500 ms, QTc prolongation >60 ms, or dysrhythmias are encountered.
- Conditions known to provoke torsades de pointes, especially hypokalaemia and extreme bradycardia, should be avoided in patients with drug-induced QT prolongation.
- Exposure to other QT-prolonging drugs should be minimized in patients treated with potentially QT-prolonging chemotherapy.

---


Corresponding authors: Jose Luis Zamorano, Head of Cardiology, University Hospital Ramon Y. Cajal, Carretera De Colmenar Km 9.100, 28034 Madrid, Spain. Tel: +34 91 336 85 15, E-mail: zamorano@secardiologia.es; and Patrizie Lancellotti, University of Liège Hospital, GIGA Cardiovascular Sciences, Departments of Cardiology, Heart Valve Clinic, CHU Sart Tilman, Liège, Belgium and Gruppo Villa Maria Care and Research, Anthesa Hospital, Bari, Italy. Tel: +32 4 366 7194 Fax: +32 4 366 7195, E-mail: plancellotti@chu.ulg.ac.be

Special thanks to Daniel Rodriguez Muñoz for his contribution.