

## How-to treat Chemotherapy-Induced Cardiotoxicity

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*In the last decade cancer therapy has had an enormous progress leading to an important reduction of morbidity and mortality of several types of cancer.*

*The therapeutic management of patients with cancer includes a combination of drugs, radiation therapy, and surgery, but cardiovascular toxicity is a potential short- or long-term complication of various anticancer therapies.*

**Topic(s):** Prevention

### Key Questions:

1. Anticancer drugs and cardiotoxicity .....	1
2. Screening of cancer patients.....	1
3. How to do it? .....	2
4. Key library .....	3

### 1. Anticancer drugs and cardiotoxicity

Some drugs, such as anthracyclines or other biological agents, have been implicated in causing potentially irreversible clinically cardiac dysfunction, which can negatively impact the quality of life as well as the prognosis of oncologic patients.

The new generation targeted therapies are considered less toxic and better tolerated by patients compared with classic chemotherapy agents, but serious unexpected side effects on myocardial function have been described, and longer follow-up is needed to determine the exact profile and outcomes of related cardiac side effects.

Currently, 17% of patients have to stop cancer therapy due to heart involvement.

Some of these side-effects are irreversible (Type I), leading to progressive CV disease, and some others induce reversible dysfunction (Type II), with no long-term cardiac damage to the patient. Assessment of the prevalence, type and severity of cardiac toxicity caused by various cancer treatments is a breakthrough topic for patient management.

The cardiotoxic risk increases with the high cumulative anticancer drugs doses, anticancer drugs dose intensity, and radiotherapy, which, in patients with cancer treated with anticancer drugs, can exacerbate anticancer drugs-induced cardiac tissue damage.

### 2. Screening of cancer patients

The early detection of cardiotoxicity is a critical issue for patients undergoing chemotherapy, and more are the advantages in identifying cardio toxicity early.

This would help select patients who would benefit from cardio protective regimens, so that heart failure does not become an obstacle to the oncologist during therapy, and to the patient during his/her survival.

a. The 1st screening of cancer patients to find their susceptibility to anticancer drugs-cardiotoxicity includes:

- a comprehensive medical history
- a complete physical examination
- cardiac biomarkers troponin and B-type natriuretic peptide (BNP)
- electrocardiogram
- 2D echocardiogram with Doppler at baseline for measurement of Left Ventricular Ejection Fraction (LVEF).

b. The 2nd screening of cancer patients to find their susceptibility to anticancer drugs-cardiotoxicity includes:

- MUGA (Multiple Gated Acquisition scan)
- Magnetic Resonance

### 3. How to do it?

Detecting cardio toxicity is a critical issue in the clinical setting, in order to appropriately modulate and, hopefully, not interrupt cancer therapy.

But while cardiovascular side effects such as arterial hypertension, myocardial ischemia, dysrhythmia, and thrombosis can be readily diagnosed, the assessment of cardiac dysfunction and its prognosis is more challenging.

A number of interventions are available to prevent cardiac toxicities. They include:

Prolonged infusion of systemic therapy drugs

Use of cardioprotective agents: dexrazoxane and cardioprotectant monoHER

Use of antioxidants

Use of angiotensin-converting enzyme inhibitors (ACE-I) and betablocking

#### 1. Systemic therapy drugs

Liposomal formulations of systemic therapy drugs such as pegylated doxorubicin have also been associated with a reduced risk of cardiac toxicity.

#### 2. Cardioprotective agents

Dexrazoxane (an iron chelator) :

- reduces the production of reactive oxygen species and free radicals
- significantly reduces anthracycline-related cardiotoxicity in adults with different solid tumors
- reduces anthracycline-related cardiotoxicity in children with acute lymphoblastic leukemia and Ewing's sarcoma.

Cardioprotectant monoHER in experimental studies has showed that inhibits CBR1 activity. CBR1 V88I genotype status and the type of anthracycline substrate dictate the inhibition of CBR1 activity.

MonoHER acted as a competitive CBR1 inhibitor when using daunorubicin as a substrate, acted as an uncompetitive CBR1 inhibitor for the small quinone substrate menadione.

3. **Carnitine** has been shown:

- to improve mitochondrial function
- to lower the release of cytochrome C, which in turn decreases the activation of caspase-9.

Activation of intrinsic apoptotic pathway is thus decreased, preventing cell death.

A phase II trial at the Ottawa Hospital Cancer Centre treated women receiving anthracycline as systemic therapy for stage II breast cancer with either carnitine or a placebo.

The study was closed early because of poor accrual, but the results may provide some insight into the potential role of compounds such as carnitine in the prevention of cardiac toxicity.

#### 4. ACE-I and BB

The use of angiotensin-converting enzyme inhibitors (ACE-I) and betablocking (BB) agents may be highly effective in patients with cancer who are treated with potentially cardiotoxic therapy (which represent a high-risk for the development of Heart Failure).

Carvedilol may prevent cardiac damage induced by doxorubicin due to its antioxidant activity. The effect of carvedilol was confirmed in a randomized study in which prophylactic use of carvedilol in a small population of patients treated with anthracycline prevented LVD and reduced mortality.

Nakamae et al. have demonstrated that valsartan, an angiotensin receptor blocker (ARB), given concurrently to anthracycline-containing regimens, prevents cardiac damage.

Although promising data have been published, convincing evidence from large randomized and prospective trials is still needed.

Recent findings reported in a large population of anthracycline-induced cardiomyopathy patients demonstrated that the time elapsed from the end of chemotherapy to the start of HF therapy (time-to-treatment), with ACE-I and, when tolerated, with BB, is a crucial variable for recovery of cardiac dysfunction.

Indeed, the likelihood of obtaining a complete LVEF recovery is higher in patients in whom treatment is initiated within 2 months from the end of chemotherapy.

Unfortunately these patients have been excluded from large randomized trials evaluating the effectiveness of ACE-I and BB.

Ultimately current strategies to address cardiac toxicity typically deal with exposure to a single cardiotoxic drug.

Read also Professor Greco's article: "How to prevent Chemotherapy-Induced Cardiotoxicity"

#### 4. Key library

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