Managing cardiotoxicity induced by chemotherapy in centers from low income countries

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Abstract. Cardiovascular diseases and cancer account for 60% of deaths in the Western world. They have common risk factors, such as obesity and diabetes, and are often found in the same patient. It is more common in a patient with tumour disease who develops cardiovascular involvement secondary to treatment with cytostatic or radiotherapy. A protocol of in-hospital management of cardiotoxicity induced by cytostatic is proposed with the objective of providing specialized care to patients with cancer and a history of cardiovascular disease or who develop cardiac complications during cancer therapy, in centres of low-income countries. Care and follow-up criteria are established; guidelines to identify patients who are at risk of developing cardiac dysfunction, and strategies are proposed to prevent or minimize the risk before, during and after the therapy. Finally, suggestions are presented to treat specific complications: ischemia, systemic embolism, more frequent arrhythmias, pulmonary and systemic hypertension. Ref. 42, on-line full text (Free, PDF) www.cardiologyletters.sk

Key words: cardiotoxicity – chemotherapy – cardiovascular complications

Cardiovascular diseases and cancer account for about 60% of deaths in Western countries (1). Survival rates for both diseases have increased in recent decades (1, 2); however, cardiotoxicity of cancer treatments has become increasingly frequent (1 – 3). It is a common and well-known adverse effect of many conventional cancer drugs, especially anthracyclines and chest radiation (4, 5), but it can also occur with new biologic therapies. It can affect the survival and quality of life independently of cancer prognosis (6).

It is a growing concern in clinical and preclinical trials of new medications. Adverse cardiac effects often result in interruption of cancer therapy (7). There is also an increasing need for a better prediction of the risk of cardiotoxicity of new drugs at early stage in their research (8, 9).

Though several guidelines exist on this issue, most of them are written by specialist in high income countries/regions, and doctors from middle or low income countries/regions may not have enough resources to assist these patients as these clinical guidelines state. The present manuscript, although it is far from being an official guideline, maintains the objective to lay minimum bases of Cardio-oncology consultation in centres of low-income countries.

Interdisciplinary consultation

Cardiotoxicity induced by chemotherapy is not greater than those cardiovascular affections secondary to treatment with cytostatic agents or radiotherapy defined by (10)

- Cardiomyopathy with compromise in the function of the left ventricle.
- Symptoms or signs of heart failure linked to the presence of third noise, tachycardia or both.
- Decrease of at least 5% in the ejection fraction with values lower than 55% and present signs or symptoms, or a decrease of 10% before values lower than 55% in the ejection fraction, without the presence of signs or symptoms.

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Its management must be interdisciplinary: Oncologist, Cardiologist, Psychologist, Internist should make a team (11, 12). Gastrointestinal effects that result in metabolic decontrol can be remitted to other, not included, specialists.

Main objectives of interdisciplinary consultation

Includes patients with treated, initiated, or one to be initiated (2, 13 – 15) may include:

- To provide specialized cardiac care to patients with cancer and a history of cardiovascular disease or who develop cardiac complications during cancer therapy;
- To optimize cardiac care in cancer patients undergoing potentially cardiotoxic drugs;
- To improve knowledge of cardiac complications of cancer treatments and prognosis of patients through a multidisciplinary and integrated approach that involves different health professionals (doctors, nurses and technicians);
- To promote early detection of cardiotoxicity (using clinical, laboratory and imaging biomarkers, of which echocardiography is the most important) and establish intervention strategies to optimize care.

The frequency of this consultation will depend on the prevalence of oncological diseases, treatment with chemotherapy and types of chemotherapeutic agents administered. The following criteria are proposed for cardiology evaluation (16, 17).

- Patients with high or intermediate risk for optimization of therapy (ACE inhibitors, beta blockers, statins).
- Previous treatment with doxorubicin ≥300 mg / m^2 and / or mediastinal radiotherapy ≥30 Gy.
- Structural heart disease, heart failure, coronary heart disease or arrhythmias.
- Uncontrolled hypertension, dyslipidaemia or diabetes.
- Alterations in ECG or baseline echocardiogram or during follow-up.
- Left Ventricular Ejection Fraction (LVEF) fall of > 10% with baseline LVEF ≥55% or abnormal Global Longitudinal Strain (> -19%) or > 15% fall.
- Positive biomarkers, chest pain, dyspnea, syncope, arrhythmias and refractory hypertension.

Follow-up by cardiology according to risk stratification

In March 2017, the American Society of Clinical Oncology (ASCO) (18) published guides to prevent and monitor cardiac dysfunction in adult cancer survivors. It was based on four elements:

1. Identify patients who are at risk of developing cardiac dysfunction. Hermann et al (19), from Mayo Clinic established a stratification scale which accords:

4 points: anthracycline, cyclophosphamide, ifosfamide, clofarabine, Herceptin

2 points: docetaxel, pertuzumab, sunitinib, sorafinib

1 point: bevacizumab, dasatinib, imatinib, lapatinib, myocardial disease, heart failure, coronary artery disease, diabetes mellitus, anthracycline treatment, thorax radiation, age less than 15 or over 65 years, female.

The risk of high cardiotoxicity corresponds to 6 points or more. This is divided into low (less than 3 points), intermediate (3-4 points), high (5-6 points) and very high (more than 6 points).

In addition, classification of cardiotoxicity should be carried out according to time of onset and cardiotoxicity risk of chemotherapy (20, 21):

- Time of onset:
  - Acute or subacute: when it develops from the beginning of the treatment until two weeks after it is finished.
  - Chronic: when toxicity appears after one year of completing therapy, in turn, chronic cardiotoxicity is divided into two states: early, during the first year after therapy; and late, which happens years after the completion of this.
- Cardiotoxicity risk of chemotherapy:
  - Type I: cardiotoxicity with mechanism similar to the anthracyclines "anthracycline effect". Its cardiac toxicity is dose-dependent and produces irreversible cardiac damage.
  - Type II: cardiotoxicity with mechanism similar to trastuzumab "trastuzumab effect", related to a reversible cardiac damage that allows a recovery of functionality and a restart of the regimen if indicated. This is achieved, because there are no ultrastructural changes in the myocytes.

2. Strategies to prevent or minimize risk before starting therapy. All patients receiving treatment with chemotherapy or radiotherapy should be considered as a patient with heart failure in stage A of the classification of the American Heart Association / American College of Cardiology (22).

Protocols should be adopted to reduce radiation exposure in those patients treated with radiotherapy and decisions should balance antitumor efficacy of therapy with potential for cardiotoxicity (9, 11).

If the patient receives treatment with high doses of anthracyclines, the administration of cardioprotectors that do not diminish the antitumor action can be suggested. On the other hand, if the dose of anthracyclines is low, the prophylactic use of Angiotensin Converting Enzyme Inhibitors and Beta--Blockers is recommended to avoid cardiotoxicity (23, 24).

However, the evidence in favour of primary prevention is quite limited, so officially, it is only indicated in patients with a very high risk of cardiotoxicity (25).

Risk factors control is another indication to follow. Although the studies continue to be of very few patients, large population registers in patients without cancer, show a greater survival in patients with controlled risk factors (26).

3. Measures to minimize the risk during the administration of the therapy. The use of anthracyclines with liposomal coating, which prevent entry into the myocardium without affecting the tumor penetrance with a decrease in cardiotoxicity up to 80%, compared with conventional forms, is indicated (18).

The use of analogues of anthracyclines, such as epirubicin and mitoxantrone which have a lower cardiotoxicity, should be taken into account, although due to decreased antitumor action they are not widely used (27).

The use of dexrazoxane, an iron chelating agent, inhibits the peroxidation of lipid membranes with decreased cardiotoxicity in anthracyclines. It is used at the same time as these medications, or the first dose at the beginning and the second dose when arriving at a cumulative dose of 300 mg/m^2 (14, 15).

4. Supervision of patients during and after treatment. Patients with a very high risk of developing cardiotoxicity should undergo transthoracic echocardiography (with strain if possible) in each cycle, at the end of treatment, between 3 and 6 months, per year. Optional EKG to those with high risk: it will be done every 3 cycles, at the end of the treatment, between 3 and 6 months, per year. If the risk of CIQ is intermediate, the echocardiogram will be performed in half of the cycles, at the end between 3 and 6 months, a year with optional EKG. And finally for those who classify as low risk, their follow-up will be optional as long as they remain in this classification (28).

Although the current evidence base is limited, the demonstrated benefit and centricity of exercise in other clinical populations suggest that it may also become a key feature of future programs in the oncology setting (29).

Treatment of cardiovascular complications

Ischemia: treatment of cancer, including radiation and chemotherapy, is associated with accelerated progression of coronary artery disease. The prothrombotic state of cancer predisposes to it. If ischemia is suspected, treatment should be imposed as prescribed to other patients. Patients treated with 5-Fluorouracil should have a more frequent electrical follow-up (30).

Pulmonary hypertension: can be caused directly with extrinsic compression of lung tumors, hypercoagulability, or drug induced. It is suggested to modify anticancer therapy in patients in whom type 1 pulmonary hypertension is suspected, together with treatment with calcium channel blockers or sildenafil, and monthly monitoring of the estimated pulmonary pressures (31).

Systemic hypertension: the treatment would generally require two or more hypotensive drugs at a maximum dose. The first agent is always suggested to be an inhibitor of angiotensin-converting enzyme due to its cardioprotective effect. Patients with Diltiazem or Verapamil should change to Amlodipine. An increase in blood pressure in patients undergoing cytostatic suggests the good action of the latter (4).

Pericardium diseases: 5-15% of cancer patients present it as a complication in the final stage, and it is doubled in those patients with thoracic radiotherapy (6-30%). The EKG is useful if initial suspicion is pericarditis, but in the rest of the cases, echocardiogram is suggested (32).

Patients may be asymptomatic in the early stages, or if the effusion is not large, but by increasing volume they can cause cough, dyspnea, paradoxical pulse, and hypotension. Pericardiocentesis will be performed for severe effusions or for diagnostic purposes. Excellent results are reported with the intrapericardial administration of antitumor agents, although the latter is not part of any formal indication yet (33).

Thromboembolism and deep thrombosis: the imaging methods suggested for diagnosis are computed tomography and echocardiography in the first case and compression ultrasonography for deep thrombosis. Prevention is essential in patients with cancer, given the tendency to hypercoagulability (34).

Once the diagnosis of venous thrombosis has been made, the treatment focuses on the relief of symptoms and the prevention of the propagation of emboli. Treatment should be stopped and anticoagulation should be started (preferably low molecular weight heparins). Some patients may need thrombolysis, if this is clinically indicated. The use of the new oral anticoagulants is not approved even in patients with cancer (35, 36).

QT prolongation: it is caused by abnormalities in depolarization and repolarization that can lead to torsades de pointes and sudden death. Fredericia's formula (QT / RR cubic root) is recommended by the FDA. It is normal up to 430ms in men and 450 ms in women (37, 38).

A baseline EKG should be performed on all patients at the start of treatment and at 7 days. Interactions between medications that prolong QT should be avoided at all costs (39). Diarrhea and vomiting (common side effects) give rise to disorders of the internal environment, which can prolong QT. The treatment should be suspended if the QTc reaches 500 ms^2 (39).

Bradyarrhythmias can be caused by tumors (neck masses that compress the vagus nerve, or due to treatment (5-fluorouracil, cisplatin). If escape rhythm is unional, the indication of permanent pacemaker will depend on the presence or absence of symptoms. If it is ventricular, a permanent pacemaker

should be given. In some patients, the antitumor treatment will resolve the arrhythmia, while in others, the treatment should be replaced. In those cases where a substitute is not possible, a permanent pacemaker should be placed to allow the continuation of the treatment (40, 41).

Atrial fibrillation: its handling is similar to that of patients without cancer. Always try to identify if it is caused by cancer (or its treatment) or heart disease. The CHADVASC and HASBLED scales have not been validated for these patients (42).

Conclusions

Currently there is no consensus on the management of patients with cardiotoxicity induced by chemotherapy. The prevention and interdisciplinary treatment must be applied in a way to facilitate an adequate evolution. The patient must always receive the indicated treatment, with the least number of side effects or interruptions, without affecting prognosis, either by the tumour itself or by the cardiovascular effects of antitumor drugs.

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