

An Introduction to Chemotherapy-Related Major Complications a Cardiologist Must Face

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SUMMARY

Many successful chemotherapy schemes are related to cardiac toxic effects, particularly in the long term follow up. A cardiologist assessment is increasingly asked, but the formal training in this particular field is rather poor. As cardiologists working in an Institute with a great number of patients under chemotherapy, we decided to summarize mechanisms of action and adverse effects of different drugs frequently used in oncology, through different case reports of patients who presented serious adverse reactions with difficulties in decision making. General recommendations for prevention, early diagnosis and therapeutic strategies will be discussed.

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Key words > Anthracyclines - Fluorouracil - Gemcitabine - Cardiotoxicity

Abbreviations >

MV Mechanical ventilation	ECG Electrocardiogram
CA Coronary angiography	EF Ejection fraction
LAD Left anterior descendant artery	HF Heart failure

BACKGROUND

During the last years, different pharmacologic therapy schemes for cancer treatment have widely increased, leading to either subsequent cure of the disease or clear improvement in the survival and quality of life. It is well-known that the different antineoplastic agents (antimetabolites, anthracyclines, and biologic, hormonal, alkylating and antimicrotubules agents) have potential cardiotoxicity, and several approaches have been proposed for its treatment and prevention. (1) As cardiologists working in an Oncology tertiary center we have the chance to face the “extreme” cardiovascular complications related to chemotherapy and, in turn, we are obliged to discuss the different strategies to adopt in each particular case. The aim of this revision is to discuss the physiopathological mechanisms, clinical management and outcomes associated with the use of three antineoplastic agents currently used (5-fluorouracil, anthracyclines and gemcitabine)

5-FLUOROURACIL

Cardiotoxicity of 5-fluorouracil, an antimetabolite, is related to angina-like chest pain. Angina is a common adverse event; nevertheless, acute myocardial infarction is less frequent, with an incidence of 11/

1,000 in patients without history of ischemic heart disease and 45/1,000 in patients with prior ischemic heart disease history. (2) 5-fluorouracil induces coronary spasm related to a direct effect of protein kinase C on vascular smooth muscle. (3, 4) Angina-like chest pain without changes in the electrocardiogram (ECG) is the most common adverse event associated with this antineoplastic agent, which relieves when the drug is discontinued. Serious events may require the use of nitroglycerin and calcium channel blockers. (4) However, coronary acute syndromes should be ruled out in case of prolonged episodes, and a coronary angiography (CA) should be performed to assess the presence of a complicated plaque with local thrombosis.

Case 1

A 39-year-old female patient with a poorly differentiated squamous cervical cancer, with metastasis of the lumbosacral spine and iliac crest was treated with 5-fluorouracil. She had a history of chronic headache treated with ergotamine.

During the first cycle of chemotherapy with 5-fluorouracil she complaint of intense chest pain. The ECG showed ST elevation in the anterior wall which was unresponsive to the administration of nitroglycerine. The episode ceased after intravenous treatment with diltiazem. The patient evolved with recurrent angina refractory to treatment, with ST elevation and without increase in troponin T levels (Figures A and B). The echocardiograms performed after the episodes were normal. Based on the clinical picture and on

ECG changes, the patient underwent a coronary angiography which showed normal coronary arteries.

Case 2

Patient aged 60 years, with multiple coronary risk factors (hypertension, dyslipemia and previous smoker), with a history of stable chronic angina in functional class II and with two neoplasias, who underwent several surgeries: right nephrectomy for renal cancer, total esophagectomy and partial gastrectomy due to cancer of the gastroesophageal junction. Two days after starting therapy with 5-fluorouracil, he complaint of intense oppressive chest pain, with neither changes in the ECG nor increase in enzymes levels, associated with arterial hypotesion. Myocardial perfusion scan was normal and the patient started therapy with atenolol, clopidogrel, diltiazem, aspirin and allopurinol. Once therapy with 5-fluorouracil started again, he presented a new episode of chest pain, with electrocardiographic changes (ST elevation in lateral wall) and normal levels of troponin T. A coronary angiography was performed. The study showed a severe obstruction in the left anterior descendant artery suggestive of plaque disruption, and multivessel disease. An angioplasty to the LAD artery was performed. High-dose therapy with calcium channel blockers was started in order to continue with chemotherapy. A year later, the patient presented a new episode of prolonged angina, similar to the previously described and with negative markers. A new coronary angiogram was performed; the LAD stent was patent and the other lesions remained unchanged.

ANTRACYCLINES

Antracycline drugs, such as adiramicin and doxorubicin, are prescribed for common tumors (breast cancer, lymphomas), even in children. Cardiotoxicity is related to myocardial damage, leading to heart failure (HF). Several mechanisms are responsible for myocardial dysfunction: alterations related to calcium, contractile protein synthesis, β_1 receptors, cellular apoptosis and interstitial edema. (5) Interestingly, the incidence of acute cardiotoxicity is low, but the number of patients with depressed EF increases throughout the time, especially in patients who have received high-dose therapies. Different pediatric series have reported an incidence of 7-8% in systolic dysfunction and this number increases up to 40% in adults.

Cardiotoxicity induced by these drugs has been stratified in acute, subacute and chronic.

Acute cardiotoxicity: toxicity occurring during a cycle of chemotherapy, which may be detected by the classic assessment schemes. Symptomatic heart failure is infrequent, with an incidence of 1.7/1,000 treated patients. Non-complex cardiac arrhythmias, pericardial chest pain and nonspecific ST changes have been reported.

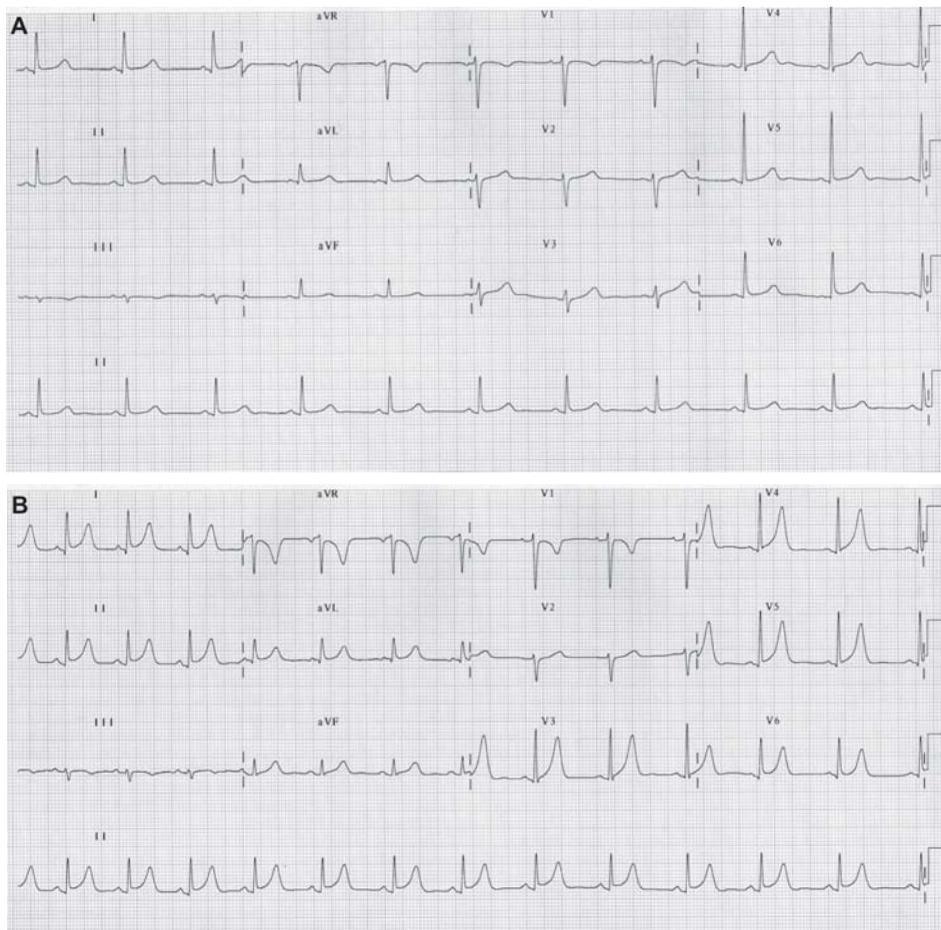


Fig. 1. A. Patient's basal ECG. **B.** ECG during 5-fluorouracil infusion. with ST elevation and positive T waves in anterior and lateral walls.

Acute and subacute cardiotoxicity: the incidence of ventricular dysfunction increases during the chronic phase, turning out to be a frequent clinical problem months or years after treatment. Mortality related to heart failure reaches 50% at 2 years. Symptoms appear at late follow-up and are associated with high risk.

Factors related to potential cardiotoxicity are age, female sex, previous irradiation, history of heart disease and individual susceptibility to drug toxicity, which is dose-independent.

Cardiotoxicity detection includes ejection fraction assessment, which should be performed prior to treatment, and strictly controlled during the course, at the end of the treatment, and once a year during late follow-up. Myocardial biopsy is useful to detect early compromise, but it should be performed only in patients with symptoms of heart failure and/or significant decrease in ejection fraction with expectations of a cure. (6, 7, 8)

Assessment of diastolic function may detect early ventricular relaxation impairment. Although diastolic dysfunction may be an early marker of reduction in the EF, it is generally reversible and disappears with the end of the chemotherapy. Table 1 summarizes the current recommendations for prevention, early detection and treatment of cardiotoxicity related to these agents. A serious case report is discussed next.

Case 3

A 53 year-old woman was admitted in several occasions with acute pulmonary edema. She had undergone mastectomy for a breast cancer, followed by chemotherapy with antracyclines and presented lumbar spine metastasis. She had no prior history of coronary risk factors or cardiovascular disease. Echocardiogram reported normal ventricular diameters, ventricular function and motility, moderate diastolic dysfunction and mitral regurgitation. Systolic function impairment was noted when heart rate exceeded 110-120 beats per minute. At the beginning, the patient had a favorable response to therapy, but, subsequently, she evolved with refractoriness to medical treatment and required mechanical ventilation (MV); a Swan-Ganz catheter was introduced to measure pulmonary capillary wedge pressure which resulted too high. Treatment with vasodilator agents, diuretics and inotropic drugs was initiated. CA was normal and endomyocardial biopsy was negative for myocarditis and cardiotoxicity for antracyclines. After several days under VM in critical condition, pulmonary capillary wedge pressure began to decrease and the patient had a favorable outcome.

This is a strange case of acute cardiotoxicity without evident lesions at the biopsy but with severe, life-threatening diastolic dysfunction.

Case 4

A patient 73 years old with a non Hodgkin lymphoma was treated with antracyclines (adriamycin and cyclophosphamide). The patient complaint of FC II dyspnea and the echocardiogram showed dilated cardiomyopathy. He started treatment with enalapril, carvedilol and spironolactone. During follow-up, EF started to decrease, most evidently 6 months after the end of chemotherapy (60%, 51%, 36 and 30%). Wall motion alterations were also present (septoapical

Table 1. Antracyclines and cardiotoxicity

Prevention of cardiotoxicity
a) Cumulative doses not to be exceeded: Doxorubicin-adriamycin 450-550 mg/m ² Daunorubicin 400-550 mg/m ² Epirubicin 650 mg/m ² Mitoxantrone 120-140 mg/m ²
b) Dexrazosane in patients with advanced breast cancer requiring high-dose therapy
Monitoring and management of cardiotoxicity
a) Prior to treatment: Left ventricle ejection fraction (LVEF) assessment by echocardiogram or radionuclide angiocardiology at rest
b) During treatment
Patients with normal initial ejection fraction
Sequential assessment of left ventricle ventricular function Every three months or with cumulative doses greater than 300 mg/m ²
Reasons to interrupt drug therapy
<i>Continuation of chemotherapy</i> Normal LVEF or a reduction up to 10%.
<i>Cessation of chemotherapy</i>
a) Decrease in LVEF by 10% to 15% in absolute value or decrease in 1-5% under the inferior normal limit, or
b) Decrease in LVEF by 16% in absolute value, irrespectively of the inferior normal limit.
Patients with initial left ventricular dysfunction
High-risk of cardiotoxicity LVEF assessment prior to each cycle
<i>Cessation of chemotherapy</i> Absolute decrease by 10% in LVEF
Severe ventricular dysfunction
Do not start treatment if basal LVEF is < 30%
Acute and subacute cardiotoxicity
LVEF assessment every 6 to 12 months after the end of the treatment
<i>Further management</i> Prescribe angiotensin-converting enzyme inhibitors if LVEF falls.

and medial, inferomedial, inferoapical, posterolmedial and posteroapical hypocinesia). Coronary angiography was normal.

This is the most typical case of progressive ventricular dysfunction after the end of the treatment, with the particularity that segment wall motion impairment was unrelated to ischemic heart disease.

GEMCITABINE

This antimetabolite is used as first-line treatment for lung cancer. Gemcitabine produces an inhibition of DNA synthesis and cellular apoptosis. Hematologic toxicity is the adverse event most frequently observed. Thrombotic microangiopathy occurs in 1/6,000 patients treated. The mechanisms involved are increased procoagulant activity, reduction in the synthesis of anticoagulant factors, stimulation of platelet aggregation and endothelial damage. This adverse event is infrequent. (9-16) Other adverse events reported are cardiac arrhythmias, lower limb edema, and dermatological and gastrointestinal events.

Case 5

A 53-year old male patient was admitted with abdominal pain associated with diarrhea and rectal bleeding. He had undergone right pneumonectomy due to lung cancer, and received adjuvant therapy with carboplatin-gemcitabine. He had no prior history of cardiovascular disease. The patient was treated with antibiotics. A CT scan reported right colon wall thickening and CBC showed increased platelet count (800,000 /mm³). Twenty four hours later he evolved with pain in the first and second right toes, with hypoesthesia, dysesthesia, and decrease in the pulse amplitude and temperature of the limb. Echo-Doppler reported obstruction of the anterior and posterior tibial arteries, and an acute arterial thrombosis was diagnosed. The patient underwent right lower limb angiography which reported occlusion of the distal popliteal artery and of the peroneal artery, and surgery was immediately performed (thrombectomy and fasciotomy). After an apparent initial recovery, the patient presented signs of reocclusion. The patient was treated with catheter thrombus aspiration, intraarterial infusion of tissue plasminogen activator, anticoagulation with heparin and clopidogrel. During evolution, several complications arose: surgical wound bleeding, hypovolemic shock, need of MV, inotropic support and blood transfusions. Finally, a supracondylar amputation of the right low limb was necessary. Screening for anticardiolipin antibodies and lupus anticoagulant was negative; C-reactive protein, free S protein, antithrombin, factor V, homocysteine, and activated protein C resistance were normal. Later, the patient recovered with favorable outcome and was discharged. Pathology of the limb showed a thrombotic state in the arteries of medium and great caliber associated with the presence of immunocomplexes. Figures 2 and 3 show a fresh thrombus in the tibial arteries, made mainly of fibrin, with few white blood cells. The vascular-nervous package presented mild to moderate muscular hyperplasia and recent microthrombi.

The histopathological substrate of treatment resistant thrombosis is similar to Virmani's description of coronary plaque "erosion" without rupture into a lipid core, with extensive adhesion to the activated surface of the thrombus.

CONCLUSIONS

Currently, clinical cardiologists face new cardiovascular disorders regarding chemotherapy as indications of these treatments have increased, leading to either subsequent cure of the disease or clear improvement in the survival and quality of life. Cardiology assessment of patients under chemotherapy is increasing,

not only in persons with underlying heart disease but also in those who have experienced certain degree of toxicity associated with these drugs. The 5 case reports reported in this revision are part of a continuum and they reflect the diversity of a problem in constant increase, as new agents such as immunomodulators also have cardiotoxic effects. (17)

Chest pain should not be underestimated in a patient receiving therapy with 5-fluorouracil. An ECG should be recorded during the episode and if electrocardiographic changes occur, the patient should be treated as if he had a conventional acute coronary syndrome.

Oncology diseases are associated with thrombotic risk, and strategies for prevention and treatment have been extensively debated. (18) The case associated with gemcitabine is exceptional and was very difficult to treat, requiring an aggressive approach which was possible due to adequate resources availability. The physiopathological substrate is interesting, regarding different hypothesis on thrombosis in atherosclerosis without evidence of endothelial damage (plaque rupture or disruption).

Cardiotoxicity related to anticyclines accounts for most cardiology consultations. We have commented on a case of acute cardiotoxicity associated with severe acute diastolic dysfunction, which was thoroughly studied, even with a myocardial biopsy. Nevertheless, subacute and chronic cardiotoxicity are more frequent and pose greater challenge. The model does not resemble a conventional cardiopathy: progressive impairment starts several months, or even years after an acute, generally undetectable aggression (without increase in troponin levels or wall motion abnormalities). The better understanding of this sequence may help us to recognize the progression of idiopathic myocardial pathology. Two Cochrane Database revisions have been published recently regarding prevention of cardiotoxicity during anticycline therapy and the lack of information available in this issue. (19, 20). In the meantime, our principal role as cardiologists consists in screening LVEF so as to detect early systolic or diastolic dysfunction, collaborating in the decision-making of new therapeutic schemes and in early treatment. Recent data of clinical trials performed on a small number of patients have demonstrated that 3-month treatment with angiotensin-converting enzyme inhibitors may revert the reduction in the ejection fraction produced by anticyclines to normal values. There is no data available regarding the use of beta blockers. The current level of knowledge recommends sequential assessment of LVEF every 6 months during the first year after treatment and then every 12 months. Screening consists of clinical consultation and LVEF assessment by echocardiogram or radionuclide angiocardiology at rest. Therapy with angiotensin-converting enzyme inhibitors should start as soon as possible if left ventricular dysfunction is detected, and

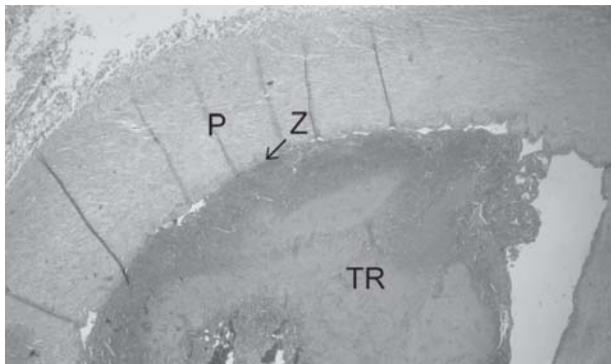


Fig. 2. Panoramic view. Recent thrombus partially attached to the vascular wall of a medium caliber artery. P: Vascular wall. TR: Recent thrombus. Arrow: Area of greater adherence. See histopathological detail of the thrombus in Figure 3. Hematoxylin-eosin x50.

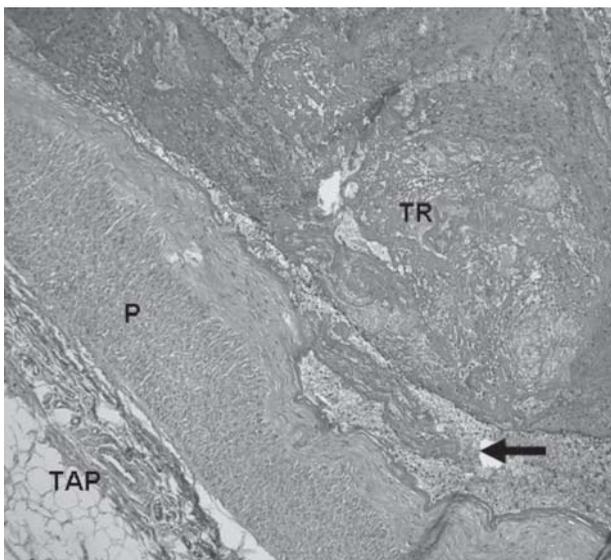


Fig. 3. Semipanoramic view of a small caliber artery with a recent thrombus with incipient recanalization. P: Vascular wall. TR: Recent thrombus. TAP: Adventitious perivascular tissue. Arrow: Area of greater adherence with endothelial surface anomalies and increased inflammation associated. Loose adherence of the thrombus and deposits of fibrinoid material. Hematoxylin-eosin x200.

with no delays in symptoms of heart failure develop. The presence of symptoms is associated with poor outcomes, even worse than in dilated cardiomyopathy of other etiologies. Dexrazoxane is a new medication studied in several clinical trials which may prevent cardiotoxicity by anthracyclines. (21) Nevertheless, its use is still restricted and debated as it may interfere with the antitumoral therapy. (22)

The challenge is open: further research is necessary to develop new strategies for prevention and treatment of these major complications. In the mean time, our contribution may be outstanding for our patients, even with the simple methods here described.

RESUMEN

Introducción a las complicaciones graves de la quimioterapia que debe enfrentar un cardiólogo

La aplicación de diferentes esquemas farmacológicos para el tratamiento oncológico ha tenido en los últimos años un gran crecimiento, en muchos casos con efectos curativos o clara mejoría de la supervivencia y la calidad de vida. Algunos esquemas incluyen drogas que pueden provocar efectos cardiotoxicos graves, lo que motiva la consulta a los cardiólogos que en la mayor parte de los casos no hemos tenido entrenamiento en esta complicación. En esta revisión se resumen mecanismos de acción y efectos adversos de diferentes drogas de uso frecuente en patología oncológica y se exponen casos clínicos con reacciones adversas graves, con dificultades en la toma de decisiones. Finalmente, se discuten los aspectos para tener en cuenta para la prevención, el control y el tratamiento de la cardiotoxicidad por agentes quimioterapéuticos.

Palabras clave > Antraciclinas - Fluorouracilo - Gemcitabina - Cardiotoxicidad

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