Consensus Statement on Diagnosis, Prevention and Treatment of Anticancer Therapy Cardiotoxicity. Brief Version

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Introduction

As life expectancy is higher as a consequence of the successful strategies used for the prevention and treatment of infectious diseases, cardiovascular diseases and cancer have become the leading causes of mortality. In Argentina, cancer accounts for 143 deaths/100000 inhabitants, a number that reaches 75 deaths/100000 inhabitants in persons < 70 years and 997 years of potential life lost/100000 inhabitants. At the same time, there is evident progress in oncology, as early diagnosis, treatment and improved survival based on the use of combined antineoplastic therapy. At the same time, such treatments have increased the incidence of immediate and late cardiac adverse events as heart failure, coronary artery spasm, microvascular disease, epicardial coronary artery ischemia, hypertension, coagulation disorders with arterial and venous thromboembolic events, pericardial or heart valve involvement, long-QT interval and arrhythmias. Improved survival of patients treated for cancer is responsible of the development of chronic heart disease in this population. This was less evident in the past as life expectancy of cancer patients was short enough to prevent the development of chronic heart diseases. Even more, at present, the risk of cardiovascular mortality can even exceed that of tumor recurrence, and cardiovascular mortality can increase eight times in surviving children. At the same time, older age adds the effects of traditional risk factors in this population. This clinical background transforms cardiotoxicity related with cancer therapy (chemotherapy and radiotherapy) in one of its main complications. Therefore, an interdisciplinary response associating oncologists' and clinicians' knowledge to that of cardiologists will be more necessary for the better management of a constantly growing chronic population. The development of this guideline should aid to extend the best diagnostic and treatment strategies for these patients, unify criteria and management, make a rationale use of the diagnostic and therapeutic resources, emphasize the value of the guidelines as a source of education and promote the exchange of information and experience between cardiology, oncology and internal medicine. In addition, the criteria here proposed are not dogmatic and should be interpreted in a flexible way, adapted to the current health conditions and available resources, which is different for each region and social stratum of our country. Therefore, in certain circumstances, these recommendations could be left aside.

A work group was integrated to cover every specific topic in which the consensus statement was divided. All the members had access to the review of this document in order to unify criteria and reduce disagreements. The following classification was used to define class recommendations agreed in this consensus:

- **Class I:** conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective. A class I

recommendation does not mean that the procedure is the only one acceptable.

- **Class II:** conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- **IIa:** weight of evidence/opinion is in favor of usefulness/efficacy.
- **IIb:** usefulness/efficacy is less well established by evidence/opinion.
- **Class III:** conditions for which there is evidence and/or general agreement that a procedure or treatment is not useful/effective and in some cases may be harmful.

Recommendations are based on the level of evidence according to the following categories:

- **Level of evidence A:** consistent evidence from randomized clinical trials or meta-analyses. It implies evaluation of multiple groups of population at risk (3 to 5). There is general consistency in the direction and magnitude of the effect.
- **Level of evidence B:** data derived from a single randomized trial, or non-randomized studies. Limited groups of population at risk have been evaluated (2 or 3).
- **Level of evidence C:** data derived from consensus opinion of experts and/or small or retrospective studies, or registries.

Definition of cardiotoxicity

The different definitions of cardiotoxicity related with cancer therapy are based on the severity of left ventricular dysfunction. Thus, cardiotoxicity can be defined in terms of a reduction in left ventricular ejection fraction as:

- Grade I: 10% to 20% decrease in ejection fraction from baseline value.
- Grade II: More than 20% reduction or below normal value (< 55%).
- Grade III: symptoms of congestive heart failure.

However, this definition has limitations. We think that the other cardiac manifestations associated with toxicity, as coronary acute syndrome, hypertension, thromboembolism, pericardial involvement, heart valve disease, arrhythmias and QT interval abnormalities should also be considered in this definition, together with congestive heart failure or asymptomatic left ventricular dysfunction. The mechanisms of collateral cardiovascular effects to antineoplastic therapy are diverse, but in the case of ventricular dysfunction, they can be subdivided into two types:

- Type I: cardiotoxicity causes cell death, so ventricular dysfunction and heart failure can develop even many years after the antineoplastic treatment has concluded. This type of cardiotoxicity is dose-dependent, has worse outcome and is associated with anthracycline drugs.
- Type II: in this case there is cardiomyocyte dys-

function without cell death and therefore ventricular dysfunction and heart failure may be reversible with absence of effects in the long-term. Therapy with trastuzumab, a monoclonal antibody specific for the HER2 protein, is an example of this toxicity.

- Understanding the differences in the mechanisms of adverse effects of cancer drugs implies that, before discontinuing the treatment, physicians should consider the difficult balance between a therapy that may save cancer patient's life in the short and mid-term and the possibility of suffering long-term adverse effects which may affect patient's survival.

Recommendations

Based on the information available, the work group makes the following recommendations.

RADIOTHERAPY

Recommendations for the evaluation and treatment of cardiotoxicity associated with radiotherapy

- Before starting, during or after radiotherapy to the chest or neck, the risk of cardiovascular complications should be assessed by:
  - age at the time of treatment;
  - radiation field received by the patient;
  - type of radiation;
  - radiotherapy plan;
  - daily and total dose;
  - total volume of the heart exposed to three dimensional conformal radiation therapy to the chest;
  - concomitant use of potentially cardiotoxic antioneoplastic drugs;
  - cardiovascular risk using any of the risk scores available (Framingham, Reynolds, Procam, Qrisks, Score Assing, Systematic COronay Risk Estimation [SCORE], Regicor, risk prediction charts for the WHO America B sub-region). The Ministry of Health and the Consensus Statement on Prevention of the Argentine Society of Cardiology recommend the use of the WHO risk chart (*Class I, Level of evidence C*).
- Strict correction of cardiovascular risk factors (hypertension, hypercholesterolemia, smoking habits, overweight or obesity and sedentary lifestyle) is recommended before starting, during or after radiotherapy to the chest or neck (*Class I, Level of evidence C*).
- Patients with history of cardiovascular disease (myocardial infarction, unstable angina, stable chronic angina, heart failure, heart valve disease, cardiomyopathies, pericardial diseases, arrhythmias, transient ischemic attack, stroke, cardiac surgery or vascular surgery) or symptoms and signs suggestive of heart disease (angina, dyspnea,

syncope, or cardiac or vascular murmurs) should undergo cardiovascular evaluation to rule out coronary artery disease, ventricular dysfunction, heart valve disease, pericardial disease, conduction system disorders or carotid artery disease before starting radiotherapy to the chest or neck (*Class I, Level of evidence C*).

- Patients > 45 years exposed to radiotherapy to the chest should undergo evaluation of coronary artery disease 5 years later with anamnesis, physical examination, ECG and stress test (exercise stress test, myocardial perfusion test or stress echocardiography) (*Class I, Level of evidence C*).

- Patients < 45 years exposed to radiotherapy to the chest should undergo evaluation of coronary artery disease 10 years later with anamnesis, physical examination, ECG and stress test (exercise stress test, myocardial perfusion test or stress echocardiography) (*Class I, Level of evidence C*).

- Patients starting, during or after receiving radiotherapy to the chest in whom coronary artery disease, ventricular dysfunction, pericardial disease, heart valve disease or conduction system disorders have been detected with or without symptoms should undergo conventional treatment of these conditions (*Class I, Level of evidence C*).

- Patients exposed to radiotherapy of the neck should undergo evaluation of carotid artery disease 5 years later with anamnesis, physical examination and carotid Doppler ultrasound (*Class I, Level of evidence C*).

- Patients exposed to radiotherapy of the chest presenting moderate cardiovascular risk (10-year cardiovascular disease risk of 10%-19%) or high cardiovascular risk (10-year cardiovascular disease risk > 20%) should undergo evaluation of coronary artery disease with anamnesis, physical examination, ECG and stress test (exercise stress test, myocardial perfusion test or stress echocardiography) (*Class IIa, Level of evidence C*).

- Patients exposed to radiotherapy of the chest presenting moderate cardiovascular risk (10-year cardiovascular disease risk of 10%-19%) or high cardiovascular risk (10-year cardiovascular disease risk > 20%) should undergo evaluation of carotid artery disease before exposure to radiotherapy with anamnesis, physical examination and carotid Doppler ultrasound (*Class IIa, Level of evidence C*).

- Evaluation of coronary artery disease, ventricular dysfunction or conduction system disorders is not recommended before radiotherapy of the chest in patients with low cardiovascular risk (10-year cardiovascular disease risk < 10%) (*Class III, Level of evidence C*).

- Evaluation of carotid artery disease is not recommended before radiotherapy of the neck in patients with low cardiovascular risk (10-year cardiovascular disease risk < 10%) (*Class III, Level of evidence C*).

HEART FAILURE

Recommendations for cardiovascular evaluation before antineoplastic therapy

- Baseline evaluation of cardiac function is recommended to all patients undergoing chemotherapy (*Class I, Level of evidence C*).

- Drug regimens with potentially cardiotoxic anticancer drugs are not recommended with LVEF $\leq$ 50% and an alternative regimen should be evaluated with the oncologist (*Class I, Level of evidence C*).

Recommendations for cardiovascular evaluation during follow-up of patients treated with anticancer drugs with type I cardiotoxic effects (anthracyclines and analogs)

- LVEF should be evaluated even in the absence of symptoms:
    - 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, or
    - after administration of a cumulative dose of 240 mg/m^2 doxorubicin or 360 mg/m^2 epirubicin in patients < 15 years or > 60 years of age (*Class I, Level of evidence C*).
    - before each administration of an anthracycline cycle and at 3, 6 and 12 months after the end of anthracycline therapy (*Class I, Level of evidence C*).

- More than 20% LVEF reduction from baseline despite normal ventricular function or 10% LVEF decline to <45% require reassessment or discontinuation of therapy and strict clinical follow-up (*Class I, Level of evidence C*).

- Assessment of cardiac function is recommended up to 10 years after anthracycline therapy in patients who were treated when they were <15 years or even >15 years of age with cumulative dose of >240 mg/m^2 doxorubicin or >360 mg/m^2 epirubicin (*Class I, Level of evidence C*).

Cardiovascular evaluation during follow-up of patients treated with anticancer drugs with type II cardiotoxic effects (trastuzumab and analogs)

- Baseline LVEF should be assessed with cardiac images before trastuzumab treatment is started and should be repeated every 3 months until completion of trastuzumab therapy and then at 12 and 18 months. Patients with symptomatic left ventricular dysfunction or more than 10% absolute decline in LVEF should undergo annual cardiac assessments (C*lass I, Level of evidence C*).

- A 16% absolute decline in LVEF or 1% to 15% LVEF decline from baseline until descent below normal limits or the development of symptoms or signs of heart failure are indications to discontinue treatment for at least 4 weeks, initiate heart fail-

ure treatment and repeat LVEF assessment. Treatment should be permanently discontinued in case of persistent LVEF decline or may be resumed if LVEF returns to normal limits (*Class I, Level of evidence C*).

- A decline in LVEF to intermediate values (< 16% absolute decline) is not an indication to discontinue treatment, but of LVEF reassessment in 4 weeks (*Class I, Level of evidence C*).
- Patients > 65 years or with hypertension who have mild baseline left ventricular dysfunction (LVEF 40-50%) should undergo interdisciplinary evaluation of the clinical context and risk-benefit ratio; treatment may be started if the potential benefits exceed the risks (*Class II, Level of evidence C*).

Recommendations for the use of biomarkers
- Biomarkers may be useful for early detection of cardiotoxicity but lack indication in routine clinical practice (*Class IIb, Level of evidence C*).

Recommendations for heart failure prevention
- Dexrazoxane is recommended in patients with metastatic disease who have received a cumulative dose of ≥ 300 mg/m² doxorubicin and have indication to continue treatment (*Class IIa, Level of evidence A*)
- Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta blockers may have a beneficial preventive effect in high-risk patients (> 50 years, with risk factors, use of high doses of anthracyclines associated with trastuzumab or radiotherapy) (*Class IIa, Level of evidence C*).

Recommendations for heart failure treatment
- Initiation of heart failure treatment (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, diuretics and aldosterone receptor antagonists) is recommended in patients with symptoms of heart failure or with asymptomatic left ventricular dysfunction (*Class I, Level of evidence A*).
- Cardiac resynchronization therapy and/or implantable cardioverter defibrillator therapy following the recommendations of the Consensus Statement of the Argentina Society of Cardiology is recommended for patients with life expectancy > 1 year (*Class IIa, Level of evidence C*).
- Cardiac transplantation is recommended in patients with heart failure refractory to medical therapy and severe left ventricular dysfunction without evidence of cancer recurrence after 5 years of the last anticancer treatment (*Class IIa, Level of evidence C*).

MYOCARDIAL ISCHEMIA

Recommendations for acute coronary syndrome treatment in patients receiving chemotherapy
- Discontinue chemotherapy, start intravenous ni-

troglycerine and oral calcium channel blockers and admission to intensive care unit (*Class I, Level of evidence C*).
- Coronary angiography in patients unresponsive to medical therapy and percutaneous coronary intervention with implantation of bare metal stent in case of severe stenosis (*Class I, Level of evidence B*).
- Medical therapy with aspirin (*Class I, Level of evidence B*), beta blockers (*Class I, Level of evidence C*), angiotensin -converting enzyme inhibitors (*Class I, Level of evidence C*) and statins (*Class I, Level of evidence C*).
- Non-cardiac surgery should be delayed for 6 weeks after implantation of a bare metal stent (*Class IIa, Level of evidence B*).
- Elective non-cardiac surgery should be delayed for 12 months after implantation of a drug-eluting stent (*Class IIa, Level of evidence B*).
- Non-cardiac surgery should be delayed for 2 weeks after balloon angioplasty (*Class IIa, Level of evidence B*).
- The use of bare metal stents is strongly recommended whenever possible (*Class IIa, Level of evidence C*).
- Preventive treatment with calcium channel blockers and nitrates (*Class IIb, Level of evidence B*).

HYPERTENSION

Recommendations for the evaluation and treatment of hypertension associated with antineoplastic agents
- Before initiating treatment with antineoplastic agents, all patients should undergo blood pressure (BP) measurement (once a week during the first 8 weeks and then every 2 to 3 weeks until the end of the treatment, followed by routine assessments) and evaluation of cardiovascular risk using any of the risk scores available (Framingham, Reynolds, Procam, Qrisks, Score Assing, Systematic COronay Risk Estimation [SCORE], Regicor, risk prediction charts for the WHO America B sub-region). The Consensus Statement on Prevention of the Argentine Society of Cardiology recommends the use WHO risk chart (*Class I, Level of evidence C*).
- Patients with hypertension (HT) before, during or after antineoplastic therapy should start antihypertensive treatment according to the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) to achieve a target blood pressure level < 140/90 (*Class I, Level of evidence C*).
- For patients whose diastolic BP increases ≥ 20 mm Hg during treatment with antineoplastic treatment, initiation of therapy according to the JNC 7 should be considered even if the absolute value is within the range of normal values (Class I, Level

of evidence C).
- Patients with hypertension and indication of angiogenesis inhibitors (AI) should have their BP controlled before initiating AI (*Class I, Level of evidence C*).
- For patients who discontinue or end treatment with AI, strict control of BP should be considered to prevent hypotension (*Class I, Level of evidence C*).
- For patients who discontinue or end treatment with AI and present hypotension, antihypertensive treatment should be discontinued (*Class I, Level of evidence C*).
- For patients undergoing treatment with AI, BP and cardiovascular risk should be periodically assessed (*Class I, Level of evidence C*).
- Patients with HT before or after antineoplastic treatment should avoid or discontinue other drugs or agents that contribute to increase BP levels (alcohol, non-steroid antiinflammatory drugs, corticosteroids, erythropoietin or sympayhomimetic drugs) (*Class II, Level of evidence C*).
- For patients treated with AI who present HT and inadequate BP control despite optimal treatment, AI dose may be reduced or temporarily discontinued (*Class II, Level of evidence C*).
- For patients treated with AI who present HT and inadequate BP control despite optimal treatment, in whom AI was temporarily discontinued, antineoplastic treatment with the same or another agent can be restarted once BP had been adequately controlled (*Class II, Level of evidence C*).
- In patients treated with AI who present grade 2-3 HT and inadequate BP control despite optimal treatment, or with history of hypertensive emergencies, AI should be permanently discontinued (*Class III, Level of evidence C*).
- Vascular endothelial growth factors (VEGF-2) (bevacizumab, suritinib, sorafenib, pazopanib and vandotanib) are contraindicated in patients with recent myocardial infarction, unstable angina, recent arterial thrombosis, uncontrolled HT, uncontrolled heart failure or long-QT interval (*Class III, Level of evidence C*).

VENOUS THROMBOSIS

Recommendations for the prevention of deep vein thrombosis associated with central venous catheters for cancer treatment
- Prevention of central venous-catheter associated thrombosis in outpatients with cancer is not recommended (*Class III, Level of evidence A*).

Recommendations for the treatment of deep vein thrombosis associated with central venous catheters for cancer treatment
- Maintenance of the central venous catheter (CVC) is justified in cancer patients with CVC associated deep vein thrombosis (DVT), in the event that the catheter is mandatory and functional (*Class IIa, Level of evidence C*).
- Anticoagulant treatment with low-molecular-weight heparin (LMVH) is recommended in cancer patients with CVC associated DVT with no contraindications to anticoagulation therapy for all the time the CVC remains in place and during 3 months after catheter removal (*Class I, Level of evidence B*).
- CVC removal and clinical surveillance is recommended in cancer patients and CVC associated DVT with contraindications to anticoagulation therapy. Once contraindications are resolved, LMWH is recommended for at least three months (*Class I, Level of evidence C*). If contraindications persist, the physician should estimate in each case the individual risk-benefit ratio of anticoagulation therapy.

Recommendations for the prevention of venous thromboembolism in outpatients with cancer receiving antineoplastic treatment
- Treatment with LMWH for the prevention of venous thromboembolism (VTE) is recommended in outpatients with cancer (e.g., solid tumors with local invasion or with metastasis) without contraindications to anticoagulation therapy who are at high risk for VTE during the whole course of chemotherapy and who agree with the risk of bleeding of anticoagulation therapy (*Class IIa, Level of evidence A*).
- Vitamin K antagonists (VKA) should not be used during chemotherapy for primary prevention of VTE in outpatients with cancer (e.g., solid tumors with local invasion or with metastasis) who have a high risk score or other additional risk factors for VTE (*Class III, Level of evidence A*).
- LMWH for primary prevention of VTE is recommended in outpatients with recent multiple myeloma without contraindications for anticoagulation therapy who are receiving AI agents (e.g., thalidomide, lenalidomide) plus dexamethasone or chemotherapy (*Class I, Level of evidence B*).

Recommendations for the prevention of venous thromboembolism in hospitalized patients with cancer receiving antineoplastic treatment
- Unfractionated heparin either bid or tid, LMWH or fondaparinux for primary prevention of VTE is recommended during hospitalization of cancer patients with reduced mobility and without contraindications for anticoagulation therapy (*Class I, Level of evidence A*).
- Graduated compression stockings or intermittent pneumatic compression devices for primary prevention of VTE is recommended during hospitalization of cancer patients with reduced mobility, active bleeding or other contraindications for anticoagulation therapy, instead of not taking VTE

preventive measures (*Class IIb, Level of evidence C*).

Recommendations for the treatment of venous thromboembolism in patients with cancer receiving antineoplastic treatment

- Venous anticoagulation treatment for VTE is recommended in cancer patients without contraindications for anticoagulation treatment, during 3-6 months and as long as the cancer is active, independently of the antineoplastic therapy received (Class I, Level of evidence B).
- Venous anticoagulation treatment is recommended in patients with active cancer at high risk of VTE and without contraindications for anticoagulation treatment, instead of not initiating therapy until objective confirmation of VTE is available (*Class IIa, Level of evidence C*).
- Initial anticoagulation treatment with intravenous LMWH, instead of VKA, is recommended for VTE in cancer patients without contraindications for anticoagulation treatment, during 3-6 months and as long as the cancer is active, independently of the antineoplastic therapy received (*Class IIa, Level of evidence B*).
- Inferior vena cava filter is recommended in cancer patients with DVT and contraindications for anticoagulation treatment and for those with recurrent pulmonary embolism (PE) despite adequate anticoagulation treatment, independently of having received or not antineoplastic therapy *(Class I, Level of evidence B)*.
- Thrombolysis is recommended in carefully selected cancer patients with massive PE and hypotension (systolic blood pressure < 90 mm Hg), without high risk of bleeding, independently of receiving or not antineoplastic therapy (*Class IIa, Level of evidence B*).

ARRHYTHMIAS AND LONG -QT INTERVAL

Recommendations for the detection and treatment of long-QTc interval and/or arrhythmias associated with chemotherapy treatment

- All patients should be evaluated with ECG before initiating chemotherapy with potentially cardiotoxic agents to detect arrhythmias and estimate baseline QTc. ECG should be repeated 7 days after initiating chemotherapy, after dose adjustment or every two months during chemotherapy (*Class I, Level of evidence C*).
- Patients presenting acute atrial fibrillation should receive pharmacological cardioversion with oral class IC antiarrhythmic drugs, intravenous amiodarone or vermakalant in the absence of structural heart disease, or intravenous amiodarone in case of structural heart disease (*Class I, Level of evidence A*).
- Electric cardioversion should be applied to patients with acute atrial fibrillation of high ventricular response associated with myocardial ischemia, hypotension or congestive heart failure, and absence of immediate response to pharmacological therapy (*Class I, Level of evidence C*).
- Patients with chronic atrial fibrillation should receive beta blockers or nondihydropyridine calcium channel blockers (verapamil or diltiazem) for heart rate control (*Class I, Level of evidence C*).
- Patients with chronic atrial fibrillation should receive low molecular weight heparin or oral anticoagulation agents according to the $CHADS_2$ or CHA_2DS_2VASc scores (*Class I, Level of evidence C*).
- Patients with complete atrioventricular block who must continue with antineoplastic therapy should receive definite pacemaker implantation (*Class I, Level of evidence C*).
- Patients with long QTc > 450 ms should have serial ECGs and electrolyte and associated medication assessment, without interrupting chemotherapy (*Class I, Level of evidence C*).
- Asymptomatic patients with long QTc > 500 ms should be hospitalized in intensive care unit with chemotherapy discontinuation, continuous ECG monitoring, evaluation of electrolytes and associated medication and serial ECGs until QTc is < 470 ms or declines 30 ms. Treatment with an antineoplastic drug different from the one likely to have prolonged the QTc interval is recommended. Treatment with the same antineoplastic drug likely to have prolonged the QTc interval should be restarted only in exceptional cases when the drug cannot be replaced by another one (*Class I, Level of evidence C*).
- Patients with long QTc > 500 ms and symptoms or sudden death should be hospitalized in intensive care unit with chemotherapy discontinuation, continuous ECG monitoring, evaluation of electrolytes and associated medication and serial ECGs until QTc is < 470 ms or declines 30 ms. Treatment with an antineoplastic drug different from the one likely to have prolonged the QTc interval is recommended. Treatment with the same antineoplastic drug likely to have prolonged the QTc interval should not be restarted (*Class I, Level of evidence C*).

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