ANMCO/AIOM/AICO Consensus Document on clinical and management pathways of cardio-oncology: executive summary

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Cardiovascular disease and cancer are leading causes of death. Both diseases share the same risk factors and, having the highest incidence and prevalence in the elderly, they often coexist in the same individual. Furthermore, the enhanced survival of cancer patients registered in the last decades and linked to early diagnosis and improvement of care, not infrequently exposes them to the appearance of ominous cardiovascular complications due to the deleterious effects of cancer treatment on the heart and circulatory system. The above considerations have led to the development of a new branch of clinical cardiology based on the principles of multidisciplinary collaboration between cardiologists and oncologists: Cardio-oncology, which aims to find solutions to the prevention, monitoring, diagnosis and treatment of heart damage induced by cancer care in order to pursue, in the individual patient, the best possible care for cancer while minimizing the risk of cardiac toxicity. In this consensus document we provide practical recommendations on how to assess, monitor, treat and supervise the candidate or patient treated with potentially cardiotoxic cancer therapy in order to treat cancer and protect the heart at all stages of the oncological disease.

Cardiovascular diseases and cancer often share the same risk factors and can coexist in the same individual. Such possibility is amplified by the deleterious effects of cancer treatment on the heart. The above considerations have led to the development of a new branch of clinical cardiology, based on multidisciplinary collaboration between cardiologist and oncologist: the cardio-oncology. It aims to prevent, monitor, and treat heart damages induced by cancer therapies in order to achieve the most effective cancer treatment, while minimizing the risk of cardiac toxicity. In this paper, we provide practical recommendations on how to assess, monitor, treat and supervise patients treated with potential cardiotoxic cancer therapies.

**Introduction**

Cardiovascular (CV) disease and cancer are the cause of about two-thirds of all deaths worldwide. Due to the progressive aging of the population the eventuality that a same individual may be affected by both, CV and cancer, is not uncommon. The association, indeed, is not casual, cancer and heart diseases may share the same risk factors, and such chance is amplified by cardiovascular complication of oncologic therapy that can lead to premature morbidity and death of cancer survivors. The above considerations have led to the development of a new branch of clinical cardiology: the cardio-oncology, a discipline based on the collaboration among cardiologists, oncologists and other medical specialists in order to find solutions for the prevention, monitoring, diagnosis and treatment of heart damage before, during and after antitumour treatments. In this Executive Summary we point out the major key points in order to achieve the most effective cancer treatment, while minimizing the risk of cardiac toxicity.

**The assessment of the cardiovascular risk**

Many oncolgic drugs have cardiotoxic effects (Table 1) often exacerbated by the presence of a pre-existing heart disease (clinical or subclinical) or by the presence of traditional CV risk factors. The estimation of CV risk profile of patients (Table 2) is valuable in cardio-oncology and should be integrated with data related to tumour treatment, in order to improve the choice on the most appropriate chemotherapy protocol and on the best cardio-protective therapy as well as to perform the most appropriate monitoring measures to schedule the follow-up. The CV risk factors should be treated with appropriate primary and secondary prevention measures according with the most recent guidelines on cardiovascular prevention of the European Society of Cardiology (ESC).
| Class                      | Drug                  | Indication          | Incidence |
|----------------------------|-----------------------|---------------------|-----------|
|                            |                       |                     | QT elongation | Systolic dysfunction | Hypertension | Myocardial ischaemia | Thromboembolism |
|                            |                       |                     |             |                    |             |                     |             |
| Anthracyclines             | Daunorubicin          | Leukemia            | ++ / +++ | ✓                    | +            | –                    | –            |
|                            | Adriamycin            | Breast, Lymphomas, Sarcomas | ++ / + | ✓                    | ++ / +++ | –                    | –            |
|                            | Liposomial adriamycin | Lymphomas, Sarcomas | +        | ✓                    | –            | –                    | + / ++ / +++ |
|                            | Epirubicin            | Breast, Stomach     | –        | ✓                    | –            | –                    | ✓            |
|                            | Idarubicin            | Leukemia            | ++ / +++ | ✓                    | ++ / +++ | –                    | –            |
|                            | Mitoxantrone          | Leukemia            | ++ / +++ | ✓                    | ++ / +++ | +                    | +            |
|                            |                       |                     |             |                    |             |                     |             |
| Alkylating agents          | Cisplatin             | Bladder, HNC, Lung, Ovary | ✓        | ✓                    | ✓            | ✓                    | +            |
|                            | Cyclophosphamide      | Hemat. Breast       | –        | –                    | ✓            | –                    | +            |
|                            | Ifosfamide            | Cervix Sarcomas     | ✓        | –                    | +++         | –                    | –            |
|                            | Antimicrotubules agents | Docetaxel          | Breast Lung | + / + | ✓                    | +++         | ++                    | +            |
|                            |                        | Nabh-Paclitaxel     | Breast Pancreas | + / + | ✓                    | –            | –                    | –            |
|                            |                        | Paclitaxel          | Breast Lung | +        | ✓                    | +            | –                    | +            |
|                            | Capecitabine          | Colon-Rectum Breast | ✓        | ✓                    | ✓            | –                    | ++ / + + +   |
|                            | 5-Fluorouracil        | Gastrointestinal    | ✓        | ✓                    | +            | –                    | + / + + +    |
| Hormone therapy            | Abiraterone           | Prostate            | ++        | –                    | ++ / +++ | ++                    | –            |
|                            | Anastrozole           | Breast              | –        | –                    | +++         | ++                    | +            |
|                            | Exemestane            | Breast              | –        | –                    | ++          | –                    | +            |
|                            | Letrozole             | Breast              | –        | –                    | ++ / +++ | ++                    | +            |
|                            | Tamoxifen             | Breast              | –        | ✓                    | + / +++ | ++                    | +            |
|                            | Target therapy with monoclonal antibody | Bevacizumab | Colon-Rectum Breast | + | ✓ | + / + | +++ | + / + | + / ++ / +++ |
|                            |                        | Brentuximab         | Lymphomas | – | – | – | – | ++ |
|                            |                        | Cetuximab           | Colon-Rectum HNC | ++ | – | ✓ | ++ | ✓ | + / + |
|                            |                        | Iplilimumab         | Melanoma | – | – | – | – | – | – | – | – |
|                            |                        | Panitumumab         | Colon-Rectum | ✓ | – | – | ++ | ++ | + |
|                            |                        | Pertuzumab          | Breast | – | – | + | – | – | – |
|                            |                        | Rituximab           | Hemat. | ✓ | – | – | ++ | ++ | ++ |
|                            |                        | Trastuzumab         | Breast Stomach | + | – | + / + | +++ | + | – | + / + |
|                            | Target therapy with small molecules | Bortezomib | Multiple myeloma | + | – | – | + / + | ++ | – | + |
|                            | Dasatinib (TKI)       | Leukemia            | ++ / +++ | + / + | ++ | ++ | ++ | + | + / + |
|                            | Erlotinib (TKI)       | Lung                | ✓ | – | – | – | ++ | + |
|                            | Gefitinib (TKI)       | Lung                | ✓ | – | – | – | ++ | + |
|                            | Imatinib (TKI)        | CMC                 | – | – | + / + | – | +++ | + |
|                            | Lapatinib (TKI)       | Breast              | ✓ | ++ | ++ | – | – | – |
|                            | Nilotinib (TKI)       | CMC                 | ++ | ++ | ++ | – | ✓ | + |
|                            | Pazopanib (TKI)       | RCC                 | – | – | + | +++ | + / + | + |
|                            | Sorafenib (TKI)       | RCC, HCC            | + | ✓ | + | +++ | ++ | + |
|                            | Sunitinib (TKI)       | GIST, RCC           | + | + | + / +++ | +++ | ++ | + / + |
|                            |                        | Vemurafenib (TKI)   | Melanoma | + | ✓ | + | ++ | ++ | + |
|                            |                        | Lapatinib (TKI)     | Breast | ✓ | – | – | ++ | ++ | + |
|                            |                        | Bortezomib          | Multiple myeloma | + | – | – | + / + | ++ | – | + |
|                            |                        | Dasatinib (TKI)     | Leukemia | ++ / +++ | + / + | ++ | ++ | + | + / + |
|                            |                        | Erlotinib (TKI)     | Lung | ✓ | – | – | ++ | + |
|                            |                        | Gefitinib (TKI)     | Lung | ✓ | – | – | ++ | + |
|                            |                        | Imatinib (TKI)      | CMC | – | – | + / + | – | +++ | + |
|                            |                        | Lapatinib (TKI)     | Breast | ✓ | ++ | ++ | – | – | – |
|                            |                        | Nilotinib (TKI)     | CMC | ++ | ++ | ++ | – | ✓ | + |
|                            |                        | Pazopanib (TKI)     | RCC | – | – | + | +++ | + / + | + |
|                            |                        | Sorafenib (TKI)     | RCC, HCC | + | ✓ | + | +++ | ++ | + |
|                            |                        | Sunitinib (TKI)     | GIST, RCC | + | + | + / +++ | +++ | ++ | + / + |
|                            |                        | Vemurafenib (TKI)   | Melanoma | + | ✓ | + | ++ | ++ | + |
|                            |                        | Everolimus          | RCC | – | – | + | ++ | ++ | + |
|                            |                        | Lenalidomide        | Multiple myeloma | + | + | + | ++ | ++ | + | + / + |
|                            |                        | Temsirolimus        | RCC | – | ✓ | – | ++ | ++ | + |

* Selected examples on the frequency of use of the drug; ++++, >10%; ++, 1-10%; +, <1% or rare; ✓, observed but the precise incidence has not been well established; –, complication not reported; CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; Emat., haematological; HF, heart failure; HNC, cancer of the head and neck; RCC, carcinoma of the kidney; TKI, tyrosine kinase inhibitor.
Hypertension is the most frequent, with potential LV dysfunction and HF. Targeted agents (lapatinib, pertuzumab, and trastuzumab) appear to be similar to that of trastuzumab.9

Cardiotoxic cardiomyopathy is difficult to treat and has a relatively poor prognosis if not promptly diagnosed.14 Among the imaging techniques, a predominant role is played by echocardiography, a non-invasive, repeatable, available and relatively inexpensive technique.9 The ejection fraction (EF) is the echocardiographic parameter most frequently used to monitor heart health. Significant declines of EF often may occur at a later time with irreversible cardiac damage. One of the aims of clinical research is to find the best technique able to identify the early cardiac damage before it produces alterations of the common ventricular contractility indexes, and then before the cardiac damage becomes irreversible (Table 4). In the recent years, Global Longitudinal Strain (GLS) technique, assessed using automated speckle-tracking echocardiography (STE), has emerged for detecting and quantifying LV dysfunction. A drop of 10% from baseline is very largely reversible upon treatment discontinuation and proper therapy.9

Table 2  Patient-related risk factors for cardiotoxicity

| What to look                                      | What to evaluate                                             | How to treat                                           |
|--------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------|
| Known heart disease                              | Present/absent<sup>a</sup>                                  | Implement primary/secondary prevention measures provided for by the Guidelines |
| Prior exposure to cardiotoxic chemotherapy and/or mediastinal radiotherapy | Present/absent<sup>b</sup>                                  | In case of exposure in asymptomatic patient evaluate the cardiovascular status (ventricular function, silent ischaemia, valves disease) |
| Smoke                                            | Pack/year<sup>c</sup>                                       | Quit                                                  |
| Alcohol consumption                              | Daily Units                                                 | Abstention or moderate use (1-4 U/die)                |
| Physical activity                                | Weekly hours                                                | Encourage mild to moderate aerobic activity (at least 3-5 h/week) |
| Blood pressure                                   | High blood pressure                                         | Search ventricular hypertrophy                        |
| Obesity                                           | Calculate body mass index                                   | Give priority to drugs with proven cardioprotective action (ace-i/ARBs, beta-blockers) |
| High blood sugar                                 | Post-prandial glycaemia (2 h) or glycolated haemoglobin and blood glucose ≤ 125 mg/dL but > 100 mg/dL | Weight reduction with the Mediterranean diet          |
| Abdominal circumference<sup>d</sup>              | Establish whether there is a metabolic syndrome             | Implement dietary program and exercise when carbohydrate intolerance, encourage the use of metformin in the case of type II diabetes |
| Lipid profile                                    | Total cholesterol, HDL cholesterol, triglycerides            | Implement dietary program and exercise, statins      |
| Renal function<sup>e</sup>                       | Creatinine, eGFR                                             | Low-protein, low-salt diet, treat high blood pressure and dyslipidaemia |

<sup>a</sup>Define the type, severity and clinical stability in relation to the oncology care program.
<sup>b</sup>Life span threshold of high-risk: prior anthracyclines exposure (adriamycin 250-300 mg/m<sup>2</sup> epirubicin 600-800 mg/m); radiation exposure (35-50Gy). In the case of radiation define whether he was involved the left hemithorax.
<sup>c</sup>Is obtained by multiplying the number of cigarette packs (20 cigarettes) smoked per day by the number of years of smoking.
<sup>d</sup>≥102 cm men; >90 cm in women.
<sup>e</sup>Renal dysfunction = eGFR <60 ml/min.

Heart failure

Heart failure (HF) is a very common complication of antineoplastic treatments and may occur with several classes of anticancer drugs7–9 (Table 1). Table 3 shows the risk factors for anthracyclines cardiotoxicity that may lead also to late onset cardiomyopathy.10,11 Other conventional chemotherapies, cyclophosphamide, cisplatin, ifosfamide, and taxanes (paclitaxel and docetaxel), can rarely induce left ventricular dysfunction (LVD) and HF. Immunotherapies and targeted therapies (Table 1) can, also, cause LVD and HF. Moreover, concomitant use of anthracyclines with trastuzumab, a monoclonal antibody directed against the receptor HER2/ErbB2, especially in cancer patients with high CV risk, may lead to severe cardiotoxicity effects.7–9,12,13 Nevertheless, trastuzumab-related cardiomyopathy is not dependent on cumulative dose and is considered to be reversible upon treatment discontinuation and proper therapy.9 The cardiotoxicity risk of other anti-HER2/ErbB2 targeted agents (lapatinib, pertuzumab, and trastuzumab-emtansine) appears to be similar to that of trastuzumab.9 Vascular endothelial growth factor (VEGF) inhibitors can cause reversible or irreversible cardiac side effects: arterial hypertension is the most frequent, with potential LVD and HF.

Management

Cardiotoxic cardiomyopathy is difficult to treat and has a relatively poor prognosis if not promptly diagnosed.14 Among the imaging techniques, a predominant role is played by echocardiography, a non-invasive, repeatable, available and relatively inexpensive technique.9 The ejection fraction (EF) is the echocardiographic parameter most frequently used to monitor heart health. Significant declines of EF often may occur at a later time with irreversible cardiac damage. One of the aims of clinical research is to find the best technique able to identify the early cardiac damage before it produces alterations of the common ventricular contractility indexes, and then before the cardiac damage becomes irreversible (Table 4). In the recent years, Global Longitudinal Strain (GLS) technique, assessed using automated speckle-tracking echocardiography (STE), has emerged for detecting and quantifying LVD. A drop of 10% from baseline is very largely abnormal and may represent subclinical dysfunction in order to consider cardioprotection also in patients without the classic criteria of cardiotoxicity (LVEF < 50%). It has been largely demonstrated that this technique is very promising to monitor the effects of cardioprotection.

Biomarkers (Table 5), also, may be used as ‘red flags’ to encourage a close clinical and instrumental monitoring and treatment. The same biomarker assay may be used for continued screening throughout the treatment pathway and substantial increases during follow-up may anticipate asymptomatic LVD in high CV risk patient treated with potentially cardiotoxic chemotherapy. Nevertheless at present the evidence to establish the interpretation of subtle variation is insufficient and their role as exclusive...
### Table 3  Risk factors of anthracyclines cardiotoxicity

| Risk factor                        | Description                                                                 |
|-----------------------------------|-----------------------------------------------------------------------------|
| Cumulative dose (life-span)       | Total cumulative dose (Adriamycin: >450 mg/m²; epirubicin: >900 mg/m²) markedly increases the risk in the long-term cardiotoxicity |
| Duration of follow-up             | The risk increases with prolonged survival for doses >250 mg/m²              |
| Rate of administration            | The risk of acute cardiotoxicity is lower with slow rate of infusion        |
| Individual dose                   | Single high doses increase the risk of late onset toxicity                   |
| Type of anthracycline             | The liposomal anthracyclines are less cardiotoxicity                        |
| Radiotherapy                      | Prior or concomitant administration (>30 Gy) increases the risk of cardiotoxicity |
| Complementary chemotherapy        | Trastuzumab, bevacizumab, paclitaxel, alkylating agents (cyclophosphamide, ifosfamide, melphalan), bleomycin, vincristine, paclitaxel, docetaxel |
| Pre-existing cardiovascular risk factors | Hypertension, ischaemic heart disease, valvular heart disease, previous cardiotoxic treatments |
| Comorbidity                       | Diabetes mellitus, chronic obstructive pulmonary disease, renal dysfunction, liver failure, obesity, dysthyroidism, electrolyte disorders, sepsis |
| Age                               | Young and old are at greatest risk                                           |
| Sex                               | Women are at greater risk than men                                          |
| Additional factors                | Trisomy 21 and African American race are at greater risk                     |

### Table 4  Summary table of the instrumental parameters used to identify the damage from chemotherapy

| Method used                  | Parameter                  | Diagnostic values for cardiotoxicity                                                                 | Limits                                                                 |
|------------------------------|----------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Echocardiography             | Ejection fraction (EF)     | * Decrease >5% with EF <55% if symptomatic patient for heart failure (HF)                            | * Image quality (better with ultrasound contrast agent)                |
|                              |                            | * Decrease >10% with EF <55% if asymptomatic patient                                                 | * Dependence on the haemodynamic state                                 |
| Dobutamine stress-echo       | EF Fractional shortening (FS) | * Reduction of EF and/or FS during pharmacological stress                                            | * Intra- and inter-operator variability (better with 3D-echo)           |
| Doppler Echocardiography      | Diastolic parameters: isovolumetric relaxation time (IVRT), deceleration time (DT), E, e', E/A ratio | * Diastolic dysfunction (↓ IVRT and DT, ↓ E, e' and E/A ratio)          | * Late and irreversible alterations                                    |
| Tissue Doppler Imaging (TDI)  | Mitral annulus velocity (s') septal and lateral | * Reduction below 15 cm/sec (septal) and 20 cm/sec (lateral)                                      | * Consistent results but from small and not confirmed studies          |
| Two-dimensional Speckle Tracking echocardiography | Global longitudinal strain | * Reduction of >15% from baseline within days after chemotherapy seems to predict future decline in EF | * Discordant data on the predictive power of future dysfunction        |
| Cardiac magnetic resonance (CMR), dynamic sequences without contrast | LV and RV volumes and EF | * Improved accuracy and reproducibility in identifying drops in EF                                 | * Not recommended for monitoring                                      |
| CMR, delayed sequences after contrast agent (gadolinium) | Early (oedema) and late (fibrosis) enhancement | * Intramyocardial oedema seen during therapy with trastuzumab and ↓ FE                             | * Discordant data between different studies                           |
|                              |                            | * Fibrosis is associated with poor prognosis                                                         | * Frequent reduction of s' in pts with prior chemotherapy, without development of HF |
|                              |                            |                                                                                                      | * Need for dedicated software                                         |
|                              |                            |                                                                                                      | * Results still to be confirmed on a large scale                       |
|                              |                            |                                                                                                      | * Costs                                                                |
|                              |                            |                                                                                                      | * Availability on the territory                                       |
|                              |                            |                                                                                                      | * Results regarding prognostic significance of oedema and fibrosis to be confirmed on a large scale |
method for routinely surveillance of cardiac damage is not clearly ascertained.

**Strategies for reducing cardiotoxicity**

In the absence of definite treatments that can reverse the anthracyclines-related myocardial damage, it is important to identify new treatment strategies that prevent or minimize the potential cardiotoxic side effects (Table 6), especially in high risk patients (Table 3) that require a strict control of traditional CV risk factor.

**Ischaemic heart disease**

Radiation therapy as well as many cancer drugs can induce myocardial ischaemia\(^4,7,9\) (Tables 1 and 7).

**Fluoropyrimidine and capecitabine**

Asymptomatic ST-segment changes on ECG represents the most frequent cardiotoxic manifestation (55%). Chest pain with or without ST-segment changes is the common clinical complaint (45%) and evolution in acute coronary syndrome may occur. Patients should be closely monitored for myocardial ischaemia using regular ECG. The symptoms usually occur within the first 72 h of 5-fluorouracil (5-FU) infusion and in the first 6 days of initiation in the case of oral administration of capecitabine.\(^15\) Occasionally, 5-FU and Capecitabine toxicity appear as acute heart failure and Tako-tsubo syndrome with LV dysfunction, in such case ventricular arrhythmias and sudden death may occur. Ischaemic heart disease can also be a complication of antiangiogenic agents: bevacizumab and tyrosine kinase inhibitors (sunitinib, sorafenib, ponatinib, axitinib, pazopanib, regorafenib).\(^9\)

**Management**

In the case of fluoropyrimidine toxicity, chemotherapy should be stopped and patients hospitalized in coronary

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### Table 5  Biomarkers and risk stratification

| Marker type | Population studied | Findings and observations |
|-------------|--------------------|---------------------------|
| TnT, Tnl, hsTnT | Anthracyclines: baseline measurement, at the end of the infusion, and one month after chemotherapy | * High predictive value (mostly negative) in the high-dose anthracyclines  
* Maybe poor prognostic factor in medium and low doses |
| TnT, Tnl, hsTnT | Trastuzumab for metastatic breast cancer: baseline survey, 2 and 4 months after starting treatment | * It seems to anticipate about 2 months the development of systolic dysfunction  
* Increased positive predictive value when combined with declining global longitudinal strain  
* Results to be confirmed in larger studies |
| BPN, Nt-proBNP | Anthracyclines (breast cancer): before and after treatment | * A > 36% increase from baseline seems to correlate with LV systolic dysfunction  
* Mixed results in different studies  
* Few studies, mixed results |
| BNP, Nt-proBNP | Trastuzumab | |

### Table 6  Strategies to control the risk of cardiotoxicity

| Type of strategy | Advantages | Only retrospective studies |
|-----------------|------------|---------------------------|
| Weekly infusions (instead of three times a week) | Lower blood peaks, observed incidence of heart failure 0.8% (vs. 2.9% with traditional scheme) | Only retrospective studies |
| Prolonged infusion (>6 h) instead of rapid bolus | Lower blood peaks, reduced incidence of heart failure | Need for central venous access, with increase of costs, preparation time and care, risk of infection |
| Epirubicin | Lower volume of distribution, with greater concentration on the neoplastic tissue and less cardiotoxicity | Higher costs of doxorubicin  
* Not available studies directly comparing with free doxorubicin. |
| Liposomal anthracyclines (pegylated or non-pegylated) | Better tolerance compared with doxorubicin. Protective effect on acute cardiotoxicity |  
* Not available data on the protective effect of late toxicity  
* Equivocal increase of seconds in the long run tumours |
| Iron chelating agents (dexrazoxane) | Currently only indicated for patients with metastatic breast cancer previously treated with high doses of anthracyclines | |
intensive care if acute coronary syndrome is suspected. The administration of non-dihydropyridine calcium channel blockers (verapamil or diltiazem) and nitrates may be indicated for the frequent occurrence of coronary spasm. If there is an absolute indication on drug rechallenge, the treatment should be performed with half dose and the patients monitored closely. The association of calcium channel blockers therapy may be useful.

**Arrhythmias**

In cancer patients Heart Rhythm Disturbances (HRD) may be the result of multiple risk factors. Metabolic disorders, electrolyte disturbances, medications (e.g. antihistamines, antiemetic, anti-infective, psychotropic drugs) can affect the appearance of cardiac arrhythmias. Nevertheless, HRD are more frequent with some chemotherapies (Tables 1 and 8). 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. Treatment should be interrupted or alternative regimens considered if the QTc is >500 ms, QTc prolongation is >60 ms or arrhythmias are present. Factors as hypokalaemia, hypomagnesemia, extreme bradycardia, and QT-prolonging drugs should be minimized inpatients treated with potential QT-prolonging chemotherapy (Figure 2).

![Figure 2](image_url)

**Table 7** Chemotherapy associated with ischaemia (Modified by 14)

| Drug          | Incidence |
|---------------|-----------|
| 5-Fluorouracil| 1–68%     |
| Capecitabine  | 3–9%      |
| Paclitaxel    | <1–5%     |
| Sunitinib/Sorafenib | 2.3% |
| Erlotinib     | 2.3%      |
| Bevacizumab   | 0.6–1.7%  |
| Axitinib      | 1–2%      |
| Pazopanib     | 2%        |
| Ponatinib     | 3–20%     |

**Table 8** Arrhythmias and related mechanisms of action induced by chemotherapy drugs

| Arritmia          | Farmaco            | Meccanismo d’azione                                                                 |
|-------------------|--------------------|-------------------------------------------------------------------------------------|
| Bradycardia       | Paclitaxel, Talidomide | Interference with His-Purkinje system                                               |
| QT prolongation   | Arsenic trioxide, Tyrosine kinase inhibitors, Dasatinib, Lapatinib, Sunitinib, Vandetanib, Pazopanib, Vemurafenib, Vorinostat, Anthracyclines | Block of the potassium channels                                                     |
| Ventricular fibrillation | Capecitabine | Coronary artery spasmKounis Syndrome                                                |

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Before Treatment
Obtain a baseline ECG for QTc evaluation

Patients at risk for prolonged QTc

QTc > 500 msec.
Or
history of QTc prolongation
(congenital or acquired)

Administering Chemotherapy

ECG monitoring after 1 week or after any modification of the dose of chemotherapy

Discontinue chemotherapy if QTc > 500 msec. or if prolongation of >60 msec from baseline

Cardiological evaluation

QTc prolongation?

YES
Hold Chemotherapy

NO
Stop Chemotherapy

Figure 2 Algorithm for the evaluation and management in the course of chemotherapy with potential effect on the QT.
Arterial hypertension

Hypertension is a frequent co-morbidity in patients with cancer and may be worsened or newly induced by steroids or non-steroid anti-inflammatory drugs frequently used in oncology. Antiangiogenic agents (Table 1) can induce hypertension and degenerate to related heart complications (i.e., heart failure, myocardial ischaemia). ACE inhibitors or ARBs, beta-blockers and dihydropyridine calcium channel blockers are the antihypertensive drugs of choice. Non-dihydropyridine calcium channel blockers should preferably be avoided due to drug interactions.

Thrombo-embolic disease

Thrombo-embolism often complicates the course of cancer and recognizes different aetiological moments (Table 9). The arterial thrombotic events (ETA) in cancer can occur in case of treatment with anti-angiogenic drugs, cisplatin, VEGF inhibitors, and hormonal therapies. Ischaemia/myocardial infarction is the most common clinical manifestation. The pro-thrombotic state may facilitate embolic events secondary to atrial fibrillation. The most frequent thrombo-embolic complications in cancer patients are venous thrombo-embolism (VTE) with deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is the second cause of death in cancer patients. It may affect up to 20% of hospitalized patients and is frequently undiagnosed. A four weeks antithrombotic therapy with low molecular weight heparin (LMWH) is currently recommended for VTE prophylaxis by consensus guidelines. In the case of major surgery, systematic prophylaxis for VTE in outpatient admitted for chemotherapy is not recommended and the decision should be individualized. In stable patients LMWH given over a period of 3-6 months is the first choice for TVE therapy in cancer patients. At the moment we do not have enough data to support the use of fondaparinux or new oral anticoagulants (NOAC) for the initial treatment of acute VTE in patients with cancer. We are waiting the results of Hokusai VTE-cancer to know if edoxaban is similar to dalteparin in preventing recurrence of acute VTE following and initial index in cancer subjects. Different NOACs may differ because of potential drug interactions and sensitivity to renal or hepatic dysfunction. The use of vitamin K antagonists (VKA) in cancer patients is complicated; difficulties in maintaining a therapeutic International Normalised Ratio (INR) occur due to a variety of reasons such as drug interactions, unpredictable bioavailability, vomiting, malnutrition or diarrhea, poor compliance for repeated laboratory tests.

Surveillance in the follow-up

Cancer patients follow-up is critical for the prevention and treatment of possible late cardiovascular complications (Table 10).

Cancer patients should be aware on the possible cardiovascular risk factors, overall subjects treated with anthracyclines or mediastinal radiotherapy. At 10 years it is mandatory to perform stress test or CT coronary angiography (Figure 3). Moreover, patients should be encouraged to a healthy lifestyle. A careful surveillance is often necessary for the patients in long-term hormonal therapy. Tamoxifen may increase the risk of thrombo-embolic complications and aromatase inhibitors have been linked to increased risk of heart disease. The same applies to patients treated with androgen deprivation therapy (ADT) for prostate cancer which are prone to metabolic syndrome, diabetes, accelerated atherosclerosis, and cardiovascular events.

Consensus Document Approval Faculty

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Table 10  Suggested follow-up and treatment after cancer therapy

| Treatment performed                                      | Exams programmed                                      | Associated risk factors                       |
|----------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------|
| Anthracyclines, particularly if:                         | Echocardiogram                                         | Hypertension                                  |
| • Female                                                 | At 6-12 month of follow-up, after completion of chemotherapy |                               |
| • Age <15 years or > 60 years                            | Every 1-5 years, depending on the risk profile         | Diabetes mellitus                            |
| • Dose (Doxorubicin > 240 mg/mq; Epirubicin > 360 mg/mq) |                                                                 | Obesity                                       |
| Target therapy ± Taxanes                                 | Yearly for 5 years after the conclusion of therapy. Thereafter every 5 years | Sedentary                                    |
| Hormone therapy                                          | Clinical follow-up                                     | Smoke                                         |
| Radiation therapy to the chest/mediastinal               | Echocardiography at 6-12 month of follow-up, then every 1-5 years depending on risk profile | Alcohol consumption                          |
| if involved the left hemithorax and/or total radiation in the cardiac area ≥ 30Gy | Exercise test after 5 years and then every 3-5 years. | Kidney failure                               |
| Radiation therapy to the head/neck                       | Consider Stress-Echocardiography or coronary CT scan   |                                               |
|                                                           | Carotid artery Echo-Doppler after 3-5 years Ultrasound thyroid and periodic evaluation of thyroid hormones (FT3, FT4, TSH) |                                               |

Figure 3  Algorithm of patient management during and after radiation.

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References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S,
Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntn er P, Mussolin o ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pand ey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015 update. A report from the American Heart Association. Circulation 2015;131:e29-322.

2. Driver JA, Djoussé L, Logroscino G, Gaziano JM, Kurth T. Incidence of cardiovascular disease and cancer in advanced age: prospective cohort study. BMJ 2008;337:a2467.

3. Eyre H, Kahn R, Robertson RM, Clark NG, Doyle C, Hong Y, Gansler T, Glynn T, Smith RA, Taubert K, Thun MJ. American Cancer Society; American Diabetes Association American Heart Association. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Circulation 2004;109:3244-3255.

4. Truong J, Yan AT, Cramarossa G, Chan KK. Chemotherapy-induced cardiotoxicity: detection, prevention, and management. Can J Cardiol 2014;30:869-878.

5. Barac A, Murtagh G, Carver JR, Chen MH, Freeman AM, Hermann J, Iliescu C, Ky B, Mayer EL, Okwosa TM, Plana JC, Ryan TD, Rzeszut AK, Douglas PS. Cardiovascular health of patients with cancer and cancer survivors: a roadmap to the next level. J Am Coll Cardiol 2015;65:2739-2746.

6. Piepoli MF, Hoes AW, Clark NG, Doyle C, Hong Y, Gansler T, Glynn T, Smith RA, Taubert K, Thun MJ. American Cancer Society; American Diabetes Association American Heart Association. Cardiovascular health of patients with cancer and cancer survivors: a roadmap to the next level. J Am Coll Cardiol 2015;65:2739-2746.

7. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol 2009;53:2231-2247.

8. Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, Skopicki H, Lenihan DJ, Gheorghiea M, Lyon AR, Butler J. Cancer therapy-related cardiac dysfunction and heart failure: part 1: definitions, pathophysiology, risk factors, and imaging. Circ Heart Fail 2016;9:e002661.

9. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Abiyoz V, Asteeggiano R, Galdersi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Molyt D, Piepoli MF, Tamargo J, Torbicki A, Suter TM. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG). 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. Eur Heart J 2016;37:2768-2801.

10. Harake D, Franco VI, Henkel JM, Miller TL, Lipshultz SE. Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. Future Cardiol 2012;8:647-670.

11. Takemura G, Fujiwara H. Doxorubicin-induced cardiomyopathy from the cardiotoxic mechanisms to management. Prog Cardiovasc Dis 2007;49:330-344.

12. Tarantini L, Gori S, Faggiano P, Pulignano G, Simoncini E, Tuccia F, Cecchertini R, Bovelli D, Lestuzzi C, Cioffi G. ICARO (Italian CARdio-Oncologic) Network. Adjuvant trastuzumab cardiotoxicity in patients over 60 years of age with early breast cancer: a multicenter cohort analysis. Ann Oncol 2012;23:3058-3063.

13. Mantarro S, Rossi M, Bonifazi M, D’Amico R, Blandizzi C, La Vecchia C, Negri E, Moja L. Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer. Intern Emerg Med 2016;11:123-140.

14. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, Rubino M, Veglia F, Fiorentini C, Cipolla CM. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213-220.

15. van Es N, Di Nisio M, Boni fazi M, D’Amico R, Blandizzi C, La Vecchia C, Negri E, Moja L. Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer. Intern Emerg Med 2016;11:123-140.

16. Groarke JD, Nguyen PL, Nohria A, Ferrari R, Cheng S, Moslehi J. Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. Eur Heart J 2014;35:612-623.