Concepts in cardiac oncology

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Cardiac oncology is a subspecialty of cardiology engaging cardiologists and oncologists alike, in order to provide the best possible oncologic treatment for patients at high cardiovascular risk or developing cardio-toxicity during the course of their treatment, thus avoiding discontinuing it, and aiming at improving survival and quality of life. Early diagnosis and the effectiveness of the newer cancer treatments delivered an increasing number of long-term survivors (presently almost 30 million worldwide), at high risk of developing cardiovascular diseases. This predisposition has been correlated not only to the toxic side effects of the oncologic treatment but also to a real vulnerability to the risk factors in this patients population. For decades, the concept of cardio-toxicity in cardiac oncology has been restricted to ventricular dysfunction, but during the last few years the Food and Drug Administration has approved hundreds of new molecules and cardiac oncology has escalated its complexity. The introduction of new target therapy, proteasome inhibitors, immunomodulators, and inhibitors of the immunitary checkpoint, magnified the concept of cardio-toxicity to a wider definition of ‘cardiovascular toxicity’ incorporating arterial hypertension, ischaemia, cardiomyopathy, myocarditis, arrhythmic complications, long QT, and arterial and venous thrombosis. We are still lacking guidelines on the new and varied forms of toxicity, as well as monitoring strategies in the short- and long-term follow-up.

Ventricular dysfunction

In 2017, the ASCO guidelines were published concerning the prevention and monitoring strategies of ventricular dysfunction that defined as patients at risk, those undergoing treatment with high doses of anthracyclines and/or RT, sequential treatments of anthracyclines, and trastuzumab, treatments with doses of anthracyclines or trastuzumab but associated with two or more cardiovascular risk factors, patients aged ≥60 years, left ventricular function at the limits (FE value 50–55%), previous myocardial infarction, and moderate-severe valvulopathy. Cardio-protection strategies include the use of prolonged anthracycline infusion regimens, less cardiotoxic dexrazoxane and liposomal anthracyclines, the use of conformational modulated radiation therapy and breathing control techniques. In cardiology, the pharmacological strategies of primary prevention with the use of angiotensin-converting enzyme (ACE) inhibitors, sartans, beta blockers have not shown satisfactory results in clinical studies for a number of reasons: low number of patients enrolled, selection of low-risk populations, heterogeneity in the outcome measures, short duration of follow-ups. As part of the monitoring, it has been observed that cardiotoxicity from anthracyclines occurs in 98% of cases within 12 months and therefore an echocardiographic evaluation is necessary 6–12 months after the end of the anthracycline chemotherapy and the early treatment carried out with enalapril and beta blockers allow normalization of left ventricular function in 82% of cases even if only 11% of patients show complete recovery of ventricular function at baseline. The diagnosis of cardiotoxicity is currently defined with a >10% reduction in the ejection fraction (EF) and an absolute value of less than 53% according to the American Society of Echocardiography (ASE) and the European Society of Cardiovascular Imaging (EACVI), while the cutoff is 50% according to the European Society of Cardiology.

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yzed. Patients with cardiac toxicity were divided into four
groups: (i) normal, with both cardiac markers (Tn and N-
terminal pro B-type natriuretic peptide) within the normal
range and preserved EF; (ii) mild, with increased markers
and EF ≥50%; (iii) moderate, with EF value of 40-49% with
or without biomarkers increase; and (iv) severe, with EF
value ≤40%. Cardiac toxicity was defined as the appear-
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tricular function and was found in 37.5% of patients in the
24-month follow-up period but in only 3.1% of the cases it
was severe and significantly correlated with total mortal-
ity. The use of Tn is not part yet of the guidelines because
of a partial lack of data of cut-off value for the troponins
(troponin T, ultra-sensitive troponins), timing of with-
drawals, duration of follow-up, and definition of cardiac
eventpoints.

Trastuzumab, a humanized anti-HER2 monoclonal anti-
body, was developed for the treatment of breast cancer
women who overexpress HER2 and which represents 25% of
cases and is associated with molecular, histopathological
and clinical characteristics of aggression and unfavourable
prognosis. Trastuzumab changed the scenario of HER2 posi-
tive disease allowing improved prognosis and survival both
when used in neoadjuvant (preoperative), adjuvant (post-
operative), and in metastatic forms. Surprisingly, however,
trastuzumab caused an ‘unexpected’ cardiotoxicity re-
lated to anthracycline toxicity and potentiated when tras-
tuzumab is administered concomitantly or shortly after
anthracyclines. Monitoring should be carried out every
3 months, according to the studies that led to the approval
of the drug, if the FE value remains >50%. In centres where
the GLS is measured, a variation of more than 15% could
involve the adoption of cardio-protection strategies as
already happens in cases where the EF becomes less
than 50%. A new toxicity is emerging in recent years: myocarditis
induced by immune checkpoint inhibitors. The clinical syn-
drome associated with myocarditis is extensive and can in-
clude a spectrum of symptoms including palpitations, chest
pain, acute or chronic heart failure, pericarditis, and
pericardial effusion. In addition, myocarditis can occur in-
dolently with mild ventricular dysfunction. In diagnosis,

Vascular toxicity

The vascular toxic effects, unlike ventricular dysfunction,
are very varied and less well characterized and cancer it-
self represents a risk factor for vascular disease, above all
increasing the risk of thromboembolic events. Many tradi-
tional therapies such as fluoropyrimidines, platinum, and
radiation therapy still represent the cornerstone of many
treatment protocols today. Fluoropyrimidines 5-fluoroura-
cil and its oral pro-drug capecitabine can induce ischaemia
(angina, heart attack, arrhythmia, and sudden death) by
coronary vasospasm, endothelial damage, and endothelin
vasoconstriction, in the absence of coronary artery disease
and the symptoms are reversible upon discontinuation of
treatment and treatment with vasodilators; Platinum com-
ponents can induce vascular damage by endothelial dam-
age, platelet hyperaggregability, and reduced availability
of NO. Finally, radiation therapy can cause progressive mi-
crovascular and large vessel damage through inflammatory
mechanisms and one of the main side effects of mediastinal
radiation therapy is accelerated coronary atherosclerosis.
In addition to vascular damage, mediastinal radiation can
cause autonomic changes in the regulation of the cardio-
vascular system, valvulopathies, constrictive pericarditis,
therefore, in patients undergoing mediastinal RT, periodic
surveillance with functional non-invasive stress tests is re-
commended, which should be performed starting from
5 years after treatment. The introduction of target therapy
has significantly amplified treatment options in cancer
patients. In particular, small molecule tyrosine kinase
inhibitors, both directed towards vascular endothelial
growth factor (VEGF) (Sorafenib, Sunitinib, Pazopanib, and
Regorafenib) and towards the mutated protein Bcr-ABL
(Nilotinib, Dasatinib, and Ponatinib) that can be adminis-
tered orally, have shown efficacy for multiple types of can-
cer and have dramatically changed the natural history of
several malignant tumours but the vascular toxicities that
can occur with the new agents are manifold and include ar-
terial hypertension, pulmonary hypertension, ischaemic
arterial events such as myocardial infarction, stroke, and
ischaemic limbs, as well as venous thromboembolic events

(ESC) Position Paper. However, traditional echocardiogra-
phy with the standard measurement of the EF shows a low
diagnostic sensitivity and a low predictive value in identifi-
ing subclinical cardiotoxicity. Subclinical ventricular dys-
function can be detected early by the study of the global
longitudinal strain (GLS) even after administration of low
doses of anthracyclines (150 mg/m²) and it has been ob-
served that a reduction compared to the baseline value
>15% has a high predictive value of symptomatic and
asymptomatic ventricular dysfunction in the following
months. The use of troponin (Tn) has shown in several
studies that it is able to identify cardiotoxicity early and to
stratify the risk in the short and long term. In particular,
the persistent increase in Tn after treatment with high-
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pericardial effusion. In addition, myocarditis can occur in-
dolently with mild ventricular dysfunction. In diagnosis,
(VTE). Other classes of new cancer therapies such as immunomodulators (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib and carfilzomib) currently used in the treatment of myeloma are associated with a risk of significant vascular toxicity.8

**Hypertension**

The management of high blood pressure in patients with cancer is a very frequent problem and involves up to one-third of the patients treated, both for problems related to the age of the population and for the use of drugs, especially VEGF inhibitors and of the proteasome.

The inhibition of VEGF reduces the production of NO, suppresses vasodilating molecules such as prostacyclines and induces a rarefaction of the capillary bed with consequent hypertension. Hypertension occurs more frequently during the first months of starting therapy and careful monitoring is therefore recommended in the initial phase of the first cycle of treatment with anti-VEGF. Treatment must be undertaken even before the start of cancer therapy according to the criteria established by the recent ESC guidelines. The general practice is to avoid the calcium channel blockers diltiazem and verapamil due to the risk of drug–drug interaction related to the induction of CYP3A4 and the use of inhibitors of the ACE inhibitor and amiodarone is preferred.9

**Acute coronary syndrome management**

Cancer patients were generally excluded from clinical trials on ischaemic heart disease. In the management of acute coronary syndromes, the recommendations of the acute coronary syndrome consensus document that sets the value of 10 000 platelets (PLT) as a cut-off for aspirin therapy and 30 000 and for double antiplatelet therapy (DAPT) with aspirin and clopidogrel are of reference. Ticagrelor and prasugrel should be avoided unless the PLT number is >50 000.10 The durability of DAPT in cancer patients raises further problems that have led bare metal stent to be preferred over DES (drug-eluting stent) for decades in this population. Premature discontinuation of DAPT is often related to clinical or pharmacological problems or to the need for diagnostic or surgical procedures. However, studies conducted with the latest generation drug-eluting stent without polymer and DES have shown safety and efficacy data of DAPT for 1 month.11 From a practical point of view, patients without active disease should be treated according to general guidelines. In cases of active cancer (and mainly in the first 6 months from diagnosis) a multidisciplinary and multi-parametric assessment is necessary, that takes into account the prognosis related to cancer, the need for surgery or an invasive diagnosis in the immediate future, of drug interactions—drug and cancer-related comorbidities. The key is a multidisciplinary approach. It is essential that in acute and unstable cases, where it may not be possible to interact with the oncologist, cardiac treatment should not be delayed ‘a priori’ only on the basis of a cancer diagnosis.

**Management of venous thromboembolism**

The use of LMWH (low molecular weight heparin) has always been the reference in thromboprophylaxis and in the treatment of venous thromboembolism (VTE) of cancer. Thromboprophylaxis with direct oral anticoagulant (DOAC) in high-risk outpatients (defined as Khorana score ≥2) has recently been studied in two important clinical trials: the AVERT study conducted with apixaban (2.5 mg × 2/day) and the CASSINI with rivaroxaban (10 mg/day), both up to 180 days.12,13 When considered together, the two trials showed a significant benefit of DOACs in the prevention of VTE with a low incidence of major bleeding and the results made it possible to insert DOACs together with LMWHs in the indications of thromboprophylaxis of VTE in the latest ASCO guidelines.14 In the treatment of the initial VTE phase, the results of the Hokusai VTE cancer study conducted with edoxaban vs. dalteparin and the SELECT-D study which compared rivaroxaban vs. dalteparin demonstrated adequate efficacy and safety of DOACs.15,16 The results made it possible to insert rivaroxaban in the indications of acute phase therapy as monotherapy and edoxaban after 5–10 days of treatment with LMWH; in the long-term treatment, intended up to 6 months for rivaroxaban and 12 months for edoxaban, the use of these DOACs is envisaged in the absence of tumours with a high risk of bleeding such as gastrointestinal or genitourinary ones or of pharmacological interaction. Recently, the Caravaggio study comparing apixaban vs. dalteparin confirmed the efficacy and safety of the treatment with DOACs in cancer patients.17

**Management of atrial fibrillation**

Cancer and atrial fibrillation (AF) share a state of hypercoagulability and in patients with cancer, the risk of AF is increased. A heart rate control strategy is generally preferred in stable patients and especially in elderly patients, patients with heart disease, with good symptom control and those with an unfavourable prognosis or in palliative care.18

In the absence of specific risk stratification scales tested in cancer patients, the CHAD2S2-VASc score is used for thrombotic risk along with the HAS-BLED which must be periodically re-evaluated. In the initial evaluation, it is essential to exclude a high bleeding risk (intracranial tumour, haematological malignancies with coagulation defects, severe thrombocytopenia, severe metastatic liver disease) and therefore evaluate the thrombotic risk. The option to be proposed is that of a treatment with DOAC in the presence of CHAD2S2-VASc ≥1 in the absence of high bleeding risk;19 in cases of high thrombotic and haemorrhagic risk, the hypothesis of closing the auricle with devices can be evaluated.

For the anticoagulant treatment, the analysis of phase III subgroups of studies has shown constant safety and efficacy of DOAC in cancer patients. An analysis of ENGAGE AF-TIMI 48 included 1153 patients who had developed post-randomization cancer and showed conserved efficacy and safety of edoxaban compared to warfarin.20 Apixaban has been shown to be superior in safety and efficacy in patients.
with active cancer enrolled in ARISTOTLE compared to warfarin in reducing stroke and other thromboembolic events. 21 Observational experience has shown that rivaroxaban, when used in patients with active cancer and AF, is associated with low rates of ischaemic stroke and clinically relevant bleeding. Although there is no direct data on the use of DOAC in patients with cancer and non-valvular AF, available evidence suggests that they represent a safe and effective option. The choice must take into account age, weight, kidney function, increased risk of bleeding in patients with gastrointestinal and genitourinary tumours, the need for concomitant antiplatelet treatment and risk of interactions with anticancer drugs.

The recent ISHT recommendations propose the adoption of an individualized and shared therapeutic regimen with the patient and propose in patients already on anticoagulant treatment the continuation of the ongoing therapy, in the absence of drug interactions, with close checks of the international normalized ratio in case of vitamin K antagonists therapy. In the case of the onset of FA during chemotherapy, preference is given to DOACs except in cancer and non-valvular AF, associated with low rates of ischaemic stroke and clinically relevant bleeding associated with low molecular weight heparin in high-risk ambulatory patients with cancer: rationale and design of the CANSONI Trial. Rationale and design of the CASSINI Trial. Thromb Haemost 2017; 119:2135-2145.

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