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POINTS OF VIEW

Cardiovascular oncology: a new discipline inside internal medicine?

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Abstract Cardiovascular disease and cancer incidence and prevalence have risen over the past few decades to become the leading causes of death. On the one hand, cancer patients will be treated with cardiotoxic chemotherapies; on the other, cardiovascular patients will receive a new diagnosis of cancer and will have to face treatments that may worsen their disease. Moreover, venous thromboembolism can commonly complicate the natural course of patients with cancer in an apparently spontaneous manner or can be triggered by a clinical event such as surgery, invasive procedures, a course of chemotherapy or radiotherapy and is known to be the second cause of death in these patients who also may need to be treated for pre-existing medical conditions or comorbidities. Thus, we introduce the concept of cardiovascular oncology (in the place of cardiooncology) to underline that the problems in this field are not limited to cardiotoxicity of chemotherapies and to the interaction between cardiologists and oncologists, and we focus on the role of the Internist, the only health care giver able to face the multiple problems that cancer patients may undergo.

Keywords Cancer · Cardiotoxicity · Cardiovascular oncology · Venous thromboembolism · Internal medicine

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Introduction

Cardiovascular disease and cancer incidence and prevalence have risen over the past few decades to become the leading causes of death. Even if cardiovascular diseases are still the first cause of death, the relative impact of cancer on general mortality has increased. There are several common risk factors for both cardiovascular disease and cancer [1, 2] and a patient with a neoplasm or preneoplastic condition who undergoes cancer therapy or chemoprevention is now at a substantial risk for the deterioration of cardiovascular health. Thus, even if (and due to the fact that) survival after cancer has recently improved (in Italy over 4 % of population has had a previous diagnosis of cancer), cardiovascular problems induced by antineoplastic drugs have emerged as a relevant issue. On the one hand, patients with a healthy heart and cardiovascular system will be treated with old and new cardiotoxic chemotherapies; on the other, cardiovascular patients will receive a new diagnosis of cancer and will have to face treatments that may worsen their disease. The National Cancer Institute defines cardiotoxicity in general terms as ''toxicity that affects the heart'' (http://www.cancer.gov/dictionary). This definition embraces a variety of side effects affecting both the heart and circulation: valvular injury, dysrhythmias, changes in blood pressure (BP), arterial/venous thrombosis or impairment in myocardial contraction or relaxation (i.e., systolic and diastolic dysfunction) [2]. Thus, potential cardiovascular damage linked to anticancer agents includes QT prolongation and dysrhythmias, myocardial ischemia and infarction, hypertension, left ventricular (LV) dysfunction and heart failure (HF), arterial and venous thromboembolism [1]. But, beyond these relevant issues, it is now clear that the so-called "long-term cancer survivors" have a number of general problems in which the

Internist is deeply involved. Thus, a relevant proportion of patients hospitalized in Internal Medicine wards have a positive history for (previous or active) cancer. Over the past several years the relevance of cardiovascular problems, mainly (but not only) related to cardiac toxicity of old and new anticancer treatments, has been underlined, and cardiooncology has been founded as a new subspecialty of cardiology [1]. In Western countries there is an increasing interest for cardiooncology as an interdisciplinary field of cooperation of cardiologists and oncologists [2, 3]. On the other hand, venous thromboembolism (VTE) has been long known to be the second cause of death in cancer patients, [4] and this is considered a competence of Internists or Haematologists. Here we propose (1) the change of the recent term cardiooncology into cardiovascular oncology to underline that the problems in this field are not limited to cardiotoxicity of chemotherapies and to the interaction between cardiologists and oncologists; (2) the role of the holistic approach of the Internist, as the first partner of the oncologist in the care of "long-term cancer survivors".

Cardiovascular issues in oncology

Cytotoxic agents and targeted therapies used to treat cancer, including classic chemotherapeutic agents, monoclonal antibodies that target tyrosine kinase receptors, small molecule tyrosine kinase inhibitors and even anti-angiogenic drugs and chemoprevention agents, all affect the cardiovascular system [1, 2, 5] (Table 1). From the clinical standpoint, drug-related cardiotoxicity has been defined by the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials as one or more of the following: (1) cardiomyopathy in terms of a reduction in left ventricular ejection fraction (LVEF), either global or more severe in the septum; (2) symptoms associated with congestive heart failure (CHF); (3) signs associated with CHF (e.g., tachycardia); (4) reduction in LVEF from baseline that is in the range of less than or equal to 5 % to less than 55 % with accompanying signs or symptoms of HF, or a reduction in LVEF in the range of equal to or >10 to <55 %, without accompanying signs or symptoms [6]. Two distinct forms of myocardial dysfunction are identifiable. Type I chemotherapy-related cardiac dysfunction (CRCD), typically anthracycline-induced, is due, at least in part, to oxidative stress on cardiac muscle resulting in free radical formation and cell death; it is irreversible and typically associated with significant ultrastructural changes at biopsy. Type II CRCD (trastuzumab-induced), instead, is associated with reversible (up to 79 %) myocardial dysfunction rather than structural damage and is generally dose-related.

Table 1 Cardiac issues in oncology (modified from Hong et al. [5] Clin Cardiol 33:733–737, 2010)

1.	Left ventricle dysfunction/heart failure
2.	Cardiac ischemia
3.	Dysrhythmias and repolarization abnormalities (QT prolongation)
4.	Pericarditis
5.	Arterial hypertension

Furthermore, biological therapies that interfere with the vascular endothelial growth factor (VEGF) signalling pathway, so inhibiting tumour angiogenesis, are widely used in cancer treatment. So far, at least five VEGF targeting agents have been approved by the US Food and Drug Administration (FDA): bevacizumab, sunitinib, sorafenib, pazopanib and vandetanib. Since VEGF is a major player in the maintenance of cardiovascular homeostasis, the association between anti-angiogenic drugs and hypertension, LV systolic dysfunction and HF is not surprising.

The main clinical issue to be clarified is regarding the uncertainty surrounding definition and assessment of cardiac dysfunction. Despite universal adoption, LVEF does not represent the flawless method of evaluating cardiac functional reserve: because of its inherent subjectivity in the interpretation of LVEF as assessed by echocardiography (ECHO), a drop in this parameter does not always reflect cardiac injury. Conversely, a stable LVEF should not be taken as evidence of lack of cardiotoxicity. Moreover, there are different approaches in monitoring LVEF among trials (e.g., a single LVEF drop vs. an absolute decline of at least 10 % points from baseline). Given the inconclusive evidence from clinical experience, a step back to basic science is advisable to gain insight into mechanisms underlying cardiotoxicity [2].

The relationships between cancer and ischaemic heart disease (IHD) are complex: cancer is associated with an increased risk of arterial thrombosis (see also below), some chemotherapeutic agents have been associated with IHD, and, finally, IHD patients may receive a new diagnosis of cancer and therapeutic strategies must take into account their baseline status. Cardiac ischaemia associated with antineoplastic therapy has been most commonly described in patients who received purine analogues, such as 5-fluorouracil, topoisomerase inhibitors and antitumor antibiotics [5], or, as recently demonstrated, in patients receiving radiotherapy for breast cancer [7]. Other agents associated with cardiac ischaemia have been bevacizumab, sorafenib and taxanes [5]. Cardiac dysrhythmias have been reported with many therapeutic protocols. Among dysrhythmias, a special role is played by atrial fibrillation (AF). AF, a common finding in the elderly, can be exacerbated by anticancer treatments and may complicate the outcome of patients with malignancies as side effects of surgical or

Table 2 Systemic cancer drugs with important cardiovascular side effects (modified from Suter et al. [9], Eur Heart J 34:1102–1111, 2013)

	Class (drug)	Cardiovascular side effects
Cytostatic chemotherapeutics	Anthracyclines/ analogues	Cardiac dysfunction/heart failure
	Pyrimidine analogues	Coronary spasm/ischemia
	Alkylating agents (cisplatin)	Thrombosis
	Antimicrotubule agents (paclitaxel)	Bradycardia
Signalling inhibitors	Anti-HER2	Cardiac dysfunction
	Angiogenesis inhibitors/anti VEGF	Thrombosis, hypertension
	BCR-ABL inhibitors	Cardiac dysfunction (rare), QTc prolongation
	Anti-CD20 (rituximab)	Myocardial infarction, atrial fibrillation, tachycardia, hypo/ hypertension
	Anti-ER (tamoxifen)	Thrombosis

medical therapies. AF may be due to patient stress, but can also be induced by various cytostatic agents, such as ifosfamide, gemcitabine, melphalan, cisplatin, docetaxel, 5-fluorouracil, or etoposide, or by high doses of corticosteroids. Inflammation also plays an important role in cancer and may provide a possible explanation for a relationship between AF, inflammation and cancer [2].

Prolongation of the QT interval can lead to life-threatening cardiac dysrhythmias, including "torsade de pointes". Although not optimal, the prolongation of the QT interval represents the principal clinical surrogate marker to evaluate the dysrhythmic risk of a drug. However, in some cases, the clinical benefit of therapy in the oncologic setting may outweigh the potential risk of QT prolongation, even when the prolongation is significant, which implies special needs of patient evaluation and monitoring [8].

In particular, pericarditis has been reported in patients treated with cyclophosphamide, cytarabine and bleomycin [5].

Hypertension and cancer often coexist in the same patient, and treatment with antiangiogenic agents exacerbates hypertension, with acute and long-term effects on cardiac hypertrophy and insufficiency. Hypertension is a common adverse effect in patients who are treated with bevacizumab, sorafenib and sunitinib. The mechanism of anti-angiogenic therapy-related hypertension is not fully understood, but it is thought to be related to vascular endothelial growth factor inhibition, which, through decreased NO-synthase activity, leads to decreases in NO production in the walls of arterioles and other resistance vessels [2]. The incidence and the severity of hypertension depend on the drug regimen and underlying coexisting diseases. On the other hand, hypertension can be life-threatening (malignant hypertension) and cause systemic damage such as neurological complications, namely the reversible posterior leukoencephalopathy syndrome. However, because hypertension is an established side effect of angiogenesis inhibitors and can occur at anytime after therapy initiation, clinicians must be aware of this issue and add periodic blood pressure monitoring to standard medical care [2]. The main potentially cardiotoxic drugs and their associated cardiovascular effects are reported in Table 2 [9].

An important clinical issue in the prophylactic approach to cardiac problems in oncology is the identification of patients at high cardiovascular risk, e.g. by biomarker assessment and instrumental techniques such as echocardiography. This is an appropriate strategy to evaluate the underlying risk and to reduce morbidity and mortality associated with chemotherapy. Patient screening, optimal therapeutic schemes, cardiovascular function monitoring during treatment and management of cardiovascular adverse events are crucial in the care of cancer patients. Health systems should organize an optimal approach to these relevant issues.

Thrombosis issues in oncology

Abundant evidence is available on the relationship between cancer and VTE, whereas less documented are those with arterial thromboembolism (ATE). Recently, vascular complications, including VTE or ATE and bleeding episodes, have emerged as significant side effects of angiogenesis inhibitors, especially when administered in combination with standard chemotherapy [2]. Because cancer per se increases the risk of these events, the relative contribution of anticancer drugs is currently only partially defined. The mechanisms underlying the prothrombotic effects of cancer chemotherapy have been only partially elucidated and are likely to be multiple. Cancer cells can promote the activation of blood coagulation directly by generating thrombin, or indirectly by stimulating endothelial cells and circulating mononuclear cells to synthesize and express procoagulant factors. On the other hand, cancer chemotherapy has been shown to both amplify the prothrombotic effect of cancer cells and to cause a direct damage to vascular endothelium.

VTE can commonly complicate the natural course of patients with cancer in an apparently spontaneous manner, or can be triggered by a clinical event such as surgery, a course of chemotherapy or radiotherapy, the placement of a central venous catheter (CVC), or the use of hormonal

therapy [10, 11]. This makes clear that great importance must be given to the use of effective antithrombotic prophylaxis because VTE results in increased morbidity, mortality, medical care and costs. Current guidelines recommend antithrombotic prophylaxis for patients with cancer who are admitted to the hospital for medical illness (administered for the duration of the hospital stay) and for patients who have undergone surgery for cancer (extended for up to 5 weeks), but not for routine use in ambulatory patients receiving chemotherapy [12–15]. The risk of VTE in patients receiving chemotherapy for cancer is dependent on many contributing factors, including the site and stage of primary cancer, the type and intensity of the chemotherapeutic regimen, age, coexisting conditions and performance status [16–21]. Some recent studies have suggested that antithrombotic therapy, in particular with LMWHs, may be useful in cancer patients undergoing chemotherapy, at least in those at higher thrombotic risk [19–21]. As far as treatment is concerned, we can say that, in general, VTE among patients with cancer is treated in a similar fashion to that in other patient populations. However, the increased risk of VTE in patients with cancer, the multitude of risk factors, and the high risk of VTE recurrence and mortality pose important challenges for surgeons, oncologists, Internists and other care providers [10].

Arterial ischaemic events are less common in oncology settings and include acute coronary syndromes, ischemic strokes and peripheral artery thromboembolism. In a recent study, Tsang et al. [22] report that of the 419 patients with acute limb ischaemia, 16 (3.8 %) had an associated cancer. Moreover, arterial thrombosis in cancer patients is mainly related to spontaneous in situ thrombosis in vessels with no pre-existing vascular disease [22]. Several meta-analyses and reviews have addressed the incidences of ATE events with targeted agents, in particular if used in combination. As mentioned above , myocardial ischaemia has been reported in patients treated with fluorouracil, paclitaxel and, rarely, cisplatin, which has, also, been associated with an increased risk of strokes, recurrent peripheral arterial events and aortic thrombosis. For bevacizumab, available data consistently show an increased risk of ATE, in particular high-grade ATE, especially in older patients with underlying risk factors for thrombotic events such as hypertension, diabetes and prior history of thrombotic events [23]. As with bevacizumab, so also VEGFR tyrosine kinase inhibitors sorafenib and sunitinib are associated with a significant increase in the risk of arterial thrombosis. In these high-risk patients, standard antiplatelet therapy and the management of traditional atherosclerotic risk factors are not able to affect the prognosis.

Other internal medicine issues in oncology

Patients with cancer not only have to face their primary diagnosis, but may also need to be treated for pre-existing medical conditions or comorbidities and side effects that arise in response to the cancer itself or its treatment. It may be the role of Internist to help identify and manage comorbidities and side effects as well as educate patients on prophylaxis and treatment. Most malignancies occur in patients aged 65 or older. Actually, for lung, colon, breast and prostate cancer, at least half of newly diagnosed patients are over 65 years of age. Comorbidities are common in this population, with elderly patients having an average of 3 comorbidities. Furthermore, ageing is associated with a loss of function, which can decrease survival and necessitate modified treatment. The most common pre-existing condition observed in all patients with cancer is hypertension. Diabetes is the second most prevalent pre-existing condition in middle-aged patients, while a previous solid tumour is a frequent pre-existing condition in the very old patients. Other comorbidities, together with cardiovascular and thrombotic ones, which may occur with cancer, include chronic obstructive pulmonary disease (COPD) and other pulmonary conditions, digestive system disease, arthritis, dementia, depression and other psychiatric illnesses and osteoporosis. The prevalence and severity of some comorbidities, including dementia and CHF, increase with age. A strictly related problem is polypharmacy. Commonly reported medications taken by patients with cancer to manage comorbid conditions may include

- Anti-thrombotic agents, such as warfarin and aspirin.
- Antihypertensives.
- Medications for the relief of pulmonary disorders such as asthma and COPD.
- Pain medications including NSAIDs and opioids.
- Psychoactive medications for depression or anxiety.
- Dietary supplements.

Cancer and its treatment can cause not only several general symptoms and signs such as pain, fatigue, dyspnea, nausea, diarrhoea or constipation, weight loss (oncologists tend to take care of them when they are related to cancer

Table 3 Some internal medicine issues in oncology

1.	Thrombosis prevention and treatment
2.	Renal function
3.	Hydrosaline disequilibrium
4.	Infections
5.	Cachexya

treatment), but also more complex complications such as paraneoplastic syndromes. Because the latter may be the first signs of an occult cancer, very often they are studied by the Internists. Moreover, as cancer advances, it may metastasize to other parts of the body leading to new clinical symptoms that require a diagnostic approach. Other internist issues are related to kidney function, electrolyte balance and infections (Table 3). Comorbidities influence survival in older patients and can minimize or negate the benefit of adjuvant treatment.

Conclusions

In recent years, thanks to advances in early diagnosis and especially to substantial improvements in therapy, there has been a significant increase in the survival of cancer patients. Almost all cancers can be cured today, and survival for over 5–10 years is a reasonable goal for many patients. Cardiovascular complications are a growing problem in clinical practice that may frustrate modern oncological outcome of therapy. For this reason, a careful evaluation of the patient risk profile through a close collaboration among physicians and careful monitoring of patients are necessary for a successful treatment.

Despite significant reductions of acute phase cardiotoxicity, late onset cardiotoxicity, occurring years or decades after the last course of chemotherapy, remains a serious problem. An effective partnership between internists, cardiologists and oncologists is required if strategies for dealing with the new and unexplored field of toxicity caused by biological therapies are to be developed. The newest biological drugs tend to determine high rates of cardiovascular side effects, either acute or subacute. Nevertheless, cardiotoxicity induced by targeted therapies, after resolution of acute events, is reversible in the majority of cases, but the overall survival rate of these patients is completely unknown. As targeted drugs continue to be introduced, their side effects must be further studied. The long-term prognosis of patients who receive biological therapy must, in many cases, be re-evaluated in clinical trials with a longer follow-up. It is clear that the role of cardiologists is, in theory, in all the steps of prevention, instrumental in the diagnosis and follow-up and treatment. However, only a very few patients simply have cancer and related treatments and cardiac problems in the absence of comorbidities. Thus, the role of cardiologists is in practice limited to that of a consultant in specific, although repeated, moments of cancer patient history.

Another important issue is the primary and secondary prevention of thromboembolism, especially VTE. VTE may have serious outcomes in cancer patients and tends to recur.

Moreover, together with cardiovascular, there are several possible acute and chronic medical comorbidities in cancer patients, and this problem increases with ageing and is of special relevance in fragile patients unsuitable for or refractory to oncological treatments. In elderly patients with comorbidities, when therapeutic anti-cancer options are exhausted and the patient is sick and needs hospitalization, the role of the Internist is pivotal. The Internist is the only health care giver able to face the multiple problems the patient eventually undergoes such as infections, electrolyte disturbances and renal failure while taking into account the patient as a whole. We propose the creation of Internal Medicine units that will have special expertise in cardiovascular problems, devoted to the care of these patients in the different stages of cancer.

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