Arterial hypertension in cancer: The elephant in the room☆,☆☆

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ABSTRACT

The great therapeutical success achieved by oncology is counterbalanced by growing evidences of cardiovascular (CV) toxicity due to many antineoplastic treatments. Cardiac adverse events may cause premature discontinuation of effective oncologic treatments or occur as late events undermining the oncologic success. Arterial hypertension is both the most common comorbidity in cancer patients and a frequent adverse effect of anticancer therapies.
A pre-existing hypertension is known to increase the risk of other cardiac adverse events due to oncologic treatments, in particular heart failure. Moreover, as a strict association between cancer and CV diseases has emerged over the recent years, various analyses have shown a direct relationship between hypertension and cancer incidence and mortality. Finally, many antineoplastic treatments may cause a rise in blood pressure (BP) values, particularly the novel anti VEGF agents, this possibly compromising efficacy of chemotherapy.
Aim of this review is to revise the topic and the many aspects linking arterial hypertension and cancer, and to provide a comprehensive and practical guide of the current treatment approaches.

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1. Introduction

Cancer clinical course has been deeply modified by the striking therapeutical successes achieved in oncology. While incidence of cancer is slightly stable over recent years, cancer mortality trend is lowering [1]. For many malignancies, cancer has shift from an incurable disease to a chronic condition. An optimal contemporary management of cancer patients is not anymore linked only to survival perspectives, but also to quality of life during the years gained. However, many oncologic drugs interact with the cardiovascular (CV) system and may adversely affect outcomes. Early cardiac adverse events related to cancer treatment may prompt the premature interruption of otherwise effective anticancer therapies, and late onset cardiac events may undermine the oncologic success.

Among the multiple manifestations of cardiotoxicity, an increasing number of drugs may promote development of arterial hypertension. An effective management of hypertension related to antineoplastic treatment is of paramount importance, in order to prevent serious CV events beside ensuring blood pressure (BP) values not to lead to premature discontinuation of chemotherapy.

Also, *pre-existing* hypertension is known to increase the risk of other cardiac adverse events due to antineoplastic treatments, i.e., left ventricular (LV) dysfunction. This is an aspect of key importance, considering that many cancer patients, even only because of aging [1,2], are also affected by CV diseases. Not surprisingly, hypertension is the most common comorbidity in cancer patients [3].

Furthermore, various analyses have highlighted a possible pathophysiological link between hypertension and cancer, as hypertensive subjects appear to have higher risk of developing cancer, or at least some type of malignancies.

Aim of the present work is revise this topic and to provide a brief, comprehensive review of the current leading treatment approaches.

2. Arterial hypertension as a risk factor for cancer

In 1975 Dyer and colleagues published the first analysis suggesting an association between hypertension and cancer mortality [4]. Since

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then, several other studies investigated the relationship between cancer incidence and hypertension, cancer incidence and anti-hypertensive drugs usage, cancer mortality and hypertension. A revision of the literature is presented in the Supplementary Material (Table S1). Herein are summarized the main concepts.

The widest analysis to date comprised 577,799 subjects and found a small yet significant association between hypertension and cancer incidence in men, as well as between hypertension and cancer mortality in both men and women [5]. Two subsequent studies, one on Danish registries [6] and the other on Australian-New Zealand registries [7], also reported an association between hypertension and cancer incidence in both sexes. In contrast to these data, previous studies had revealed inconclusive. No difference in the incidence of any cancer was found in a large Finnish cohort comparing hypertensive and normotensive subjects, but a relation was seen for some type of cancer [8]. Specific malignancies have indeed been assessed more widely. Hypertension increases the risk of kidney cancer in both sexes [9]. Hypertensive women have been suggested to have higher risk for developing endometrial [8,10] and breast cancer [11]. In men, hypertension is supposed to contribute to the risk of prostate cancer as part of the metabolic syndrome [12].

The metabolic syndrome itself has been advocated as a predisposing factor for cancer development, through diverse pathways [13]. However, the relationship is debated, as it is unclear if the risk depends on metabolic syndrome per se or on its individual components [14]. It seems in fact that the link between metabolic syndrome and cancer is mainly driven by hypertension and waist circumference [15].

It cannot be excluded that the association between hypertension and cancer is due to a surveillance bias. On the other hand, it may depend, at least in part, on the pairing of lower CV mortality and development of cancer with aging. Nevertheless, some causative mechanisms have been advocated to explain why hypertensive subjects appear at higher risk for cancer. For instance, levels of vascular endothelial growth factor (VEGF), a key factor in cancer related angiogenesis, are increased in hypertensive patients, and angiotensin II stimulates its production [16,17]. Interestingly, renal cell carcinoma patients treated with anti-VEGF agents and simultaneously with angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) have showed better oncologic outcomes [18–21].

However, beyond hypertension, there is growing evidence of a 'common ground' between cancer and CV diseases. The two conditions share some risk factors, such as physical inactivity, smoking and diabetes [22,23]. At a molecular level, it has been hypothesized that the crucial shared mechanism is inflammation [22,24]. A chronic inflammatory state is present both in cancer [22–24] and in heart failure (HF) [23], and atherosclerosis is considered a chronic inflammatory disease [22,24,25]. Two central pathways of inflammation, Wnt and AMPK, play a role also in the pathogenesis of atherosclerosis and endothelial dysfunction, as well as in cancer [24].

3. Arterial hypertension as a predisposing factor for left ventricular dysfunction due to anticancer drugs

Hypertensive patients with cancer are at higher risk for developing cardiac adverse events due to antineoplastic treatments. LV dysfunction is the most concerning condition within the manifestation of cardiotoxicity. Its occurrence is variable in terms of severity, onset and timing [26].

Anthracyclines cause a dose-dependent peculiar cardiotoxicity (anthracycline induced cardiotoxicity, A-CTX). Less than 1% of cases of A-CTX are acute, whereas it generally occurs within months or years after end of treatment, and presents initially as an asymptomatic LV dilatation, with a hypokinetic evolution and then overt HF [26]. An explanation for the characteristic timing of A-CTX is proposed in the 'multiple-stress' hypothesis. Anthracyclines induced damage on cardiomyocytes and cardiac stem cells, driven mainly by production of reactive oxygen species, causing the heart to be unable to adapt or self-heal, may either

worsen a pre-existing cardiac disease or represent the substrate for subsequent insults [27,28]. Not surprisingly, the risk of A-CTX is increased in patients with a previous CV disease, and specifically hypertension [27–30]. Among women treated for breast cancer, hypertension, diabetes and coronary artery disease (CAD) were predictors of HF due to anthracycline adjuvant treatment [31]. In a cohort of elderly patients affected by diffuse large B-cell lymphoma, hypertension was the strongest predictor of HF due to doxorubicin [32]. In another study on non-Hodgkin's lymphoma patients treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), those with pre-existing hypertension were significantly more likely to develop HF [33]. Moreover, these patients more frequently underwent a dose-reduction or a discontinuation of the antineoplastic therapy or experienced a delay in treatment, implying that hypertension may also render chemotherapy less effective.

Among other anticancer regimens, less frequently causing HF, it is worth to mention trastuzumab, an inhibitor of human epidermal growth factor-receptor 2 (HER2). Its cardiotoxicity is dose-independent, manifests during chemotherapy and is usually reversible. Patients at higher risk of trastuzumab induced HF are those previously exposed to anthracyclines and those with previous LV dysfunction and hypertension [26,34].

Different manifestations of cardiotoxicity, such as myocardial ischemia and arterial thrombotic events, may be caused by other antineoplastic drugs [26,29]. An example is small tyrosine kinase agents (TKIs) used in chronic myeloid leukemia (ponatinib, nilotinib, dasatinib). It has been reported that ischemic events due to these agents tend to occur more frequently in patients with greater CV risk profile [29]. In the case of ponatinib, the presence of pre-existing CV risk factors significantly raises the risk of arterial adverse events, with hypertension playing a major role [35].

4. Arterial hypertension caused by anti-neoplastic treatments

Approximately one-third of cancer patients develop hypertension during the course of their disease. In a vast analysis on more than 25,000 cancer patients, incidence rate of new-onset hypertension was higher than 32 cases per 100 person/year, presenting across all cancer types [36]. Notably, hypertension was more frequent in patients receiving chemotherapy, irrespectively of therapy type or line of treatment.

Hypertension represents indeed a frequent CV adverse event of anticancer treatments [26]. Even though it is more frequently associated with specific antineoplastic drugs, it may also be secondary to other adjuvant treatments [37].

Below are examined antineoplastic therapies more commonly causing hypertension.

4.1. Abiraterone

Abiraterone acetate is a hormonal agent recently introduced for prostate cancer. Its strong selective inhibition of androgen steroidogenesis causes, in reverse, an excessive accumulation of steroid precursors. Adverse events related to abiraterone largely depend on the intrinsic mineralocorticoid effect of these molecules [38]. Risk of developing hypertension is significantly increased by treatment with abiraterone [39], with an occurrence in up to 20% of patients [40].

4.2. Alkilating agents

Testicular cancer survivors treated with cisplatinum are at high risk of developing hypertension [41]. This is a late and dose-dependent adverse effect, frequently occurring in the context of a metabolic syndrome [42,43]. Accordingly, these patients have been reported to have unfavorable CV profile compared to age related individuals [44]. In the analysis by Sagstuen and colleagues, more than 50% of cisplatinum treated patients were affected by hypertension [42].

4.3. Anti-VEGF agents

Virtually all patients treated with anti-VEGF agents develop an increase in BP [45] and hypertension-related adverse events may occur in up to 60% of cases [46] (Table 1). Notably, data regarding incidence of hypertension as an adverse event of anticancer treatments (and not only due to anti-VEGF agents), may not be fully reliable and may underestimate reality. This is likely due to the varying definition of hypertension in oncologic literature. Recognition of hypertension and of its severity in oncologic trials is based on the Common Terminology Criteria for Adverse Events. This system has the aim of aligning adverse events reporting, however, it underwent multiple modifications and doesn't completely comply with contemporary cardiovascular classifications [47–50].

The term anti-VEGF agents comprise two groups of drugs, humanized monoclonal antibodies that directly bind to VEGF, such as bevacizumab, and TKIs such as sorafenib and sunitinib. The main target of TKIs is the VEGF receptor 2 (VEGFR 2), but they are not totally specific. Despite this, development of hypertension has similar incidence in both groups [51].

VEGFR 2 is the most important among three VEGF receptors (VEGFRs). It promotes pro-mitotic pathways and angiogenesis, endothelial cell survival and vascular permeability. Moreover, the endothelial nitric oxide (NO) synthase enzyme is activated through VEGFR 2, leading to NO production and thus vasodilatation [27,51]. Reduction in NO, due to VEGFR 2 inhibition, produces vasoconstriction and augmented peripheral resistances [52]. NO is also involved in renal sodium homeostasis, and its impaired production may lead to sodium retention as well [52]. Among TKIs targeted toward chronic myeloid leukemia, hypertension is a rare adverse effect with the exception of ponatinib, which, in contrast, has the highest rate of secondary hypertension amid all anti-VEGF agents [35,53,54]. While other TKIs used against chronic myeloid leukemia act mainly toward BRC-ABL1, ponatinib has indeed a strong effect against VEGFR 2 [35,55].

VEGF also exerts an anti-oxidant effect. Vasodilatation and NO production are in fact favored by reduction of oxidative stress [56,57]. Recent evidences showed that by inhibiting VEGFRs signaling, an imbalance in oxidative state is induced, causing reactive oxygen species production and vascular oxidative cell damage [56].

Other mechanisms are also thought to be involved in the increase in BP due to anti VEGF agents. Firstly, anti-VEGF agents increase levels of endothelin 1, a molecule with vasoconstrictive effect. It is not clear how anti-VEGF agents directly induce this augmented secretion, but endothelial dysfunction by itself, secondary to NO reduction, may be the cause [26,52,53]. Secondly, inhibition of VEGF induces loss of small vessels and augmented peripheral resistance, a phenomenon called microcapillary rarefactions [45,52,58,59]. Rarefaction may also be functional, that is, caused by severe capillary vasoconstriction, and therefore reversible [45,60].

VEGF inhibition may cause kidney injury through several mechanisms. It results in glomerular lesions leading to proteinuria [52,61].

However, even if usually appearing together [45], proteinuria does not probably contribute to hypertension [52,57,58]. They rather appear to be two different and independent events, triggered by diverse mechanisms [57,60]. Moreover, VEGF inhibition is associated with glomerular endotheliosis and renal thrombotic microangiopathy [51,60,62]. Interestingly, also pre-eclampsia is characterized by glomerular endotheliosis, hypertension and proteinuria. Its pathogenesis is indeed related to an inhibition of VEGF due to placental secretion of sFlt-1, a soluble receptor of VEGF and of placental growth factor. Furthermore, as in hypertension due to anti-VEGF agents, high levels of endothelin 1 are seen in pre-eclampsia [52,60].

Finally, TKIs act also on the platelet-derived growth factor (PDGF) receptor. Inhibition of PDGF is known to be associated with loss of microvascular pericytes [27,57].

Elevation of BP due to anti-VEGF agents is rapid [61,62]. In the case of bevacizumab, hypertension usually appears within the first cycle of therapy [59], with a median onset time of 67 days observed in a cohort of gynaecologic cancer patients [63]. Among metastatic renal cell carcinoma patients, more than 30% of individuals developed hypertension within 30 days from the beginning of therapy with TKIs [62].

Increase in BP tends to be higher in older patients, females, those with a high BMI and with a pre-existing hypertension [61,64]. Incidence of HF during therapy with anti-VEGF agents is low, more frequently occurring in those with a previous history of hypertension, CAD or HF [26,65]. Proteinuria is not usually clinically relevant, being rarely associated with impaired renal function [62]. These data suggest that though possibly being severe, anti-VEGF agents induced hypertension is a manageable adverse effect, and that, if well treated, rarely causes complication.

Interestingly, anti-VEGF-induced hypertension represents an on-target effect of these drugs, and thus it may have a prognostic significance. Studies on metastatic colo-rectal and metastatic lung cancer patients treated with bevacizumab showed that those who developed hypertension had a better prolonged free survival [52,66,67]. In a recent analysis, bevacizumab treated patients with metastatic colo-rectal cancer who developed hypertension had higher overall survival, but this result lost its significance if patients with pre-existing hypertension were excluded from analysis [68]. Incidence of hypertension secondary to sunitinib therapy in metastatic renal cell carcinoma was related with a better outcome [53,69,70].

4.4. Carfilzomib

Proteasome inhibitors are the mainstay of therapy for multiple myeloma. Cardiac adverse effects have been reported in particular with the second-generation agent carfilzomib. In trials assessing its efficacy, incidence of new-onset hypertension was up to 25% and of HF was 10% [71–73]. These seem to be dose-dependent and reversible effects [71,74]. Risk of cardiotoxicity with proteasome inhibitors is higher in patients with greater CV risk profile [72]. A strict control of CV risk factors is recommended in multiple myeloma patients [72,75], even considering these subjects are usually elderly and receive concurrent steroid therapy. Data from follow up of phase 3 trials on carfilzomib, however, showed that the long-term risk of HF is not augmented [76]. It has been proposed that the higher risk of HF registered during therapy with carfilzomib is triggered by transient increase in BP, paired with significant hydration these patients usually receive, in susceptible high CV risk subjects [76].

4.5. Copanlisib

Copanlisib is a phosphatidylinositol 3-kinase inhibitor approved for follicular lymphoma treatment. Transient elevation in BP is a frequent adverse event of this drug [77,78]. Caution regarding BP assessment prior and post-infusion is advised in order to consider reduction or discontinuation of copanlisib, in relation to development of hypertension and to its response to anti-hypertensive therapy [79].

Table 1
Anti-VEGF agents and related incidence of arterial hypertension (modified from Brinda et al. [46]).

Anti-VEGF agent	Therapeutic target	Incidence of arterial hypertension
Bevacizumab	VEGF ligand	22–24%
Sunitinib	VEGFR, PDGFR, KIT, FLT3, CSR, RET	15–34%
Sorafenib	VEGFR, PDGFR, KIT, FLT3, RET	17–29%
Axitinib	VEGFR	40%
Pazopanib	VEGFR, PDGFR, FGFR, KIT, Itk, Lck, c-FMS	36–46%
Ponatinib	VEGFR, PDGFR, FGFR, EPH, BCR-ABL, KIT, FLT3, RET, Src, TIE2	67%
Regorafenib	VEGFR, PDGFR, FGFR, KIT, RET, BRAF	28–48%
Cabozantinib	VEGFR, KIT, FLT3, RET, MET, TRKB, AXL, TIE2	32–37%
Vandetanib	VEGFR, EGFR, RET	24%

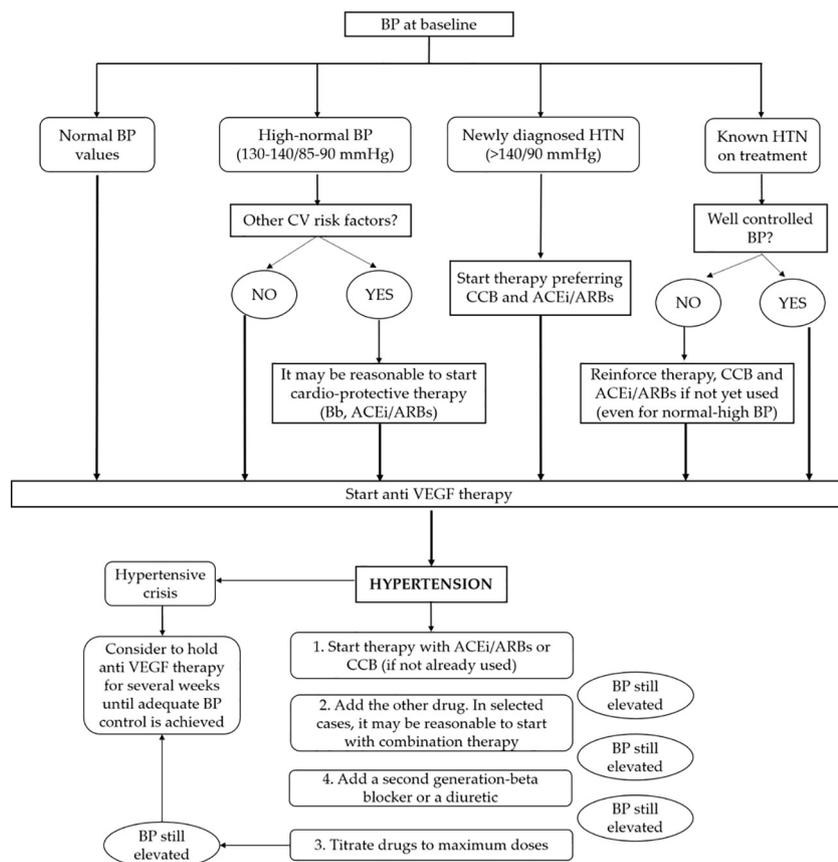## 5. Management of arterial hypertension in the cancer patient

Guidelines on the assessment of cardiac status in cancer patients are still lacking. Nevertheless, CV risk should be systematically evaluated, and some proposal in this regard have been previously published [28,34,80,81]. The topic is specifically addressed in the *2018 Guidelines for the Management of Arterial Hypertension of the European Society of Cardiology* [50].

In general population, hypertension is still not adequately tackled and controlled [2,82,83]. Its observation in a cancer patient should not be under-evaluated nor its importance be underestimated. An untreated hypertension may indeed offset the efficacy of the antineoplastic therapy and worsen the overall clinical perspective of the patient. However, it must be remembered that elevations in BP may be due to a white-coat hypertension, or to a reactive anxiety disorder. It is of great importance to investigate the patient's history, ECG and echocardiography, to avoid prescribing drugs where not necessary. Holter ambulatory BP monitoring (ABPM) or even a daily diary are useful tools. In the case of 'reactive' hypertension, anxiolytic drugs may be of great benefit.

Those individuals with a known diagnosis of hypertension must be methodically evaluated not less than patients with a new diagnosis of hypertension or those who develop hypertension after initiation of antineoplastic treatments. It is of fundamental importance to keep BP values below the recommended targets. Moreover, for patients undergoing specific regimens (i.e., anthracyclines), it may be considered to switch to anti-hypertensive drugs with a definite cardio-protective effect, such as ACEi or ARBs or second-generation beta blockers (carvedilol, nebivolol, bisoprolol), even for those with an already well controlled BP on their current therapy [28]. Although no conclusive data about primary prevention in this regard exists, it has been shown that some specific molecules may protect against effects of anthracyclines. Carvedilol is known to reduce mitochondrial dysfunction [84] and production of reactive oxygen species [85]. Furthermore, in a small study of 25 patients scheduled for antineoplastic therapy with adryamicin or epirubicin, preventive treatment with carvedilol resulted in less systolic and diastolic cardiac dysfunction at 6 months, compared to matched controls [86]. Similar results were reported for nebivolol [87], telmisartan [88] and valsartan [89]. Anthracycline-treated patients must undertake a close follow up after the end of treatment to recognize occurrence of hypertension and of LV dysfunction as soon as possible.

In the case of anti-VEGF agents, all patients, also those not affected by hypertension, should be monitored and educated, given the high probability of developing this adverse effect [90]. Their evaluation would benefit from proteinuria screening [34,61]. Some authors have also endorsed a role for ABPM to early detect hypertension occurrence [91,92]. Goal of the anti-hypertensive treatment is to reach acceptable values of BP to allow the patients to continue chemotherapy. Hypertension due to anti-VEGF agents must be dealt promptly and aggressively [17,93]. To date, no definite recommendation for therapeutic approach or comparison between anti-hypertensive drugs exist. However, ACEi or ARBs should be considered the first choice, given their reno-protective effect and the above mentioned results of favourable oncologic prognosis in renal cell cancer patients [18–21,52]. Also dihydropyridine calcium channel blockers have shown good efficacy [17,45,50]. In this view, the single pill combination with long-lasting ARBs and amlodipine at individualized dosages have been proposed as a rational approach [94,95]. Drugs increasing NO have been proposed as a valid alternative. Anyway, it should be remembered that hypertension is an on-target effect of anti-VEGF agents. NO is

Fig. 1. Algorithm for BP management in patients receiving anti-VEGF agents (*modified from: P. Spallarossa, G. Tini, D. Lenihan, Arterial hypertension. In: A. Russo et al. (Eds.), Cardiovascular Complications in Cancer Therapy. Current Clinical Pathology. Humana Press, Cham* [96]). BP: blood pressure; HTN: arterial hypertension; CV: cardiovascular; CCB: calcium-channel blockers; ACEi: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; Bb: beta blockers; VEGF: vascular endothelial growth factors.

involved in angiogenesis, and there is no demonstration that anti-hypertensive drugs which favour NO release would not compromise the anti-angiogenetic, anticancer effect of anti-VEGF agents [58]. In our opinion, anti-hypertensive medicaments targeting NO should be considered cautiously for the therapeutic use. A proposal for management of hypertension in patients treated with anti-VEGF agents is showed in Fig. 1. This approach has the advantage of guiding the patient and the referring oncologist in the management of the adverse effect, without the need for multiple re-evaluations. Moreover, since hypertension due to anti-VEGF agents has rapid onset and offset, education of the patient helps not only with up-titration of therapy but also with down-titration when anti-VEGF agents are interrupted. This way episodes of hypotension due to fixed antihypertensive therapy may be prevented.

All these recommendations are not based on specifically conducted randomized controlled trials, but mostly rely on extrapolated data and on experiences outside the oncologic field. Indeed, given the influence of CV risk factors on the development of cardiotoxicity [30–33] and experiences suggesting that hypertension as an adverse effect of antineoplastic treatments is better managed if promptly tackled [62], it may be assumed that close monitoring and treatment of hypertension is of benefit for cancer patients. Nevertheless, it cannot be excluded that in retrospective analyses the attention given to management of CV risk factors may have been variable, and hence that in cases where they were not well controlled, their influence on cardiotoxicity was greater. However, even if this was the case, we believe it represents an encouragement for a routinely dedicated CV evaluation of cancer patients prior to chemotherapy.

Finally, there is another aspect of hypertension management in the cancer patient often not sufficiently considered. Cancer itself and many antineoplastic treatments alter hemodynamic conditions, as well as sympathetic tone, renal function and electrolytes plasma values. Acting on top of this scenario, anti-hypertensive drugs may concur to produce several adverse effects:

a) Anti-hypertensive medicaments may paradoxically cause an excessive reduction in BP, with patients experiencing a worsening of symptoms, in particularly fatigue (i.e., with beta blockers usage);
b) In cancer patients, renal function is affected by several factors, such as low fluid intake due to nausea or difficult swallowing (i.e., after head-neck radiotherapy), excessive loss of fluids (diarrhoea), nephrotoxic drugs (cisplatinum). ACEi and ARBs may cause a reduction in the glomerular filtration rate and thus renal function should be cautiously monitored;
c) Some anti neoplastic drugs cause leg swelling, due to vascular leakage (i.e., imatinib), as well as some calcium channel blockers.

Clinicians must keep in mind that the complex evaluation and the dynamic management of cancer patients may even require to reduce or stop an ongoing cardio-active therapy.

6. Conclusions

Arterial hypertension in cancer patients is a clinically relevant issue.
It is fundamental not to underestimate its presence in the oncologic patient. A diagnosis of cancer should not induce to consider hypertension a less important pathological condition. Well controlled BP values reduce the risk of cardiotoxicity and of inefficacy of chemotherapies.

Moreover, hypertension itself is a common adverse event due to anticancer treatments. An early and prompt anti-hypertensive therapy is crucial to avoid discontinuation of the antineoplastic therapy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.082.

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