Review

Risk Stratification and Management of Arterial Hypertension and Cardiovascular Adverse Events Related to Cancer Treatments: An Oncology Network from Piedmont and Aosta Valley (North-Western Italy) Consensus Document

Giulia Mingrone [1,*], Elena Coletti Moia [2], Erica Delsignore [3], Gloria Demicheli [4], Paola Destefanis [5], Davide Forno [6], Giovanna Giglio Tos [7], Alessia Luciano [5], Giuliano Pinna [8], Laura Ravera [6], Antonella Fava [9], Franco Veglio [1], Oscar Bertetto [10] and Alberto Milan [1]

[1] Department of Internal Medicine and Hypertension Division, University of Turin, "Città della Salute e della Scienza" Hospital, 10126 Turin, Italy; franco.veglio@unito.it (F.V.); alberto.milan@gmail.com (A.M.)
[2] Cardio-oncology Unit, Humanitas Gradenigo Hospital, 10153 Turin, Italy; elena.colettimoia@gmail.com
[3] Internal Medicine Division, S. Andrea Hospital, 13100 Vercelli, Italy; eridelsi@tiscali.it
[4] Cardiology Department, Alliance Medical, 15100 Alessandria, Italy; gloria.demicheli@gmail.com
[5] Department of Cardiology, San Luigi Gonzaga Hospital, 10043 Turin, Italy; paoladestefanis@libero.it (P.D.); alessialuciano76@gmail.com (A.L.)
[6] Cardiology Department, Maria Vittoria Hospital, 10144 Turin, Italy; fornodavide@yahoo.com (D.F.); la_ravera@hotmail.com (L.R.)
[7] Cardiology Department, Ivrea Hospital, 10015 Turin, Italy; giovanna.giglio.tos@gmail.com
[8] Cardiology Consultant, Cottolengo Hospital, 10152 Turin, Italy; giuliano.pinna@gmail.com
[9] Division of Cardiology, Department of Cardiovascular and Thoracic, Città della Salute e della Scienza Hospital and University of Turin, 10126 Turin, Italy; antfava9@gmail.com
[10] Rete Oncologica Piemonte Valle d'Aosta Interregional Department, Città della Salute e Scienza Hospital, 10126 Turin, Italy; obertetto@cittadellasalute.to.it
* Correspondence: giulia.mingrone@edu.unito.it; Tel.: +39-011-6336953

check for updates

Abstract: Cancer patients receiving a potentially cardiotoxic oncologic therapy have an increased risk of cardiovascular adverse events (CVAEs), especially in presence of concomitant arterial hypertension (AH). Therefore, cancer patients should be evaluated before, during and after cardiotoxic treatments, to early identify new-onset or worsening AH or CVAEs. An expert panel of oncology networks from Piedmont and Aosta Valley (North-Western Italy) aimed to provide recommendations to support health professionals in selecting the best management strategies for patients, considering the impact on outcome and the risk–benefit ratio of diagnostic/therapeutic tools. We proposed an useful document for evaluating and managing AH related to cancer treatments. Patients should be divided into 4 cardiovascular (CV) risk groups before starting potentially cardiotoxic therapies: patients with low/moderate risk who should be entirely evaluated by oncologists and patients with high/very high risk who should be referred to a cardiologist or arterial hypertension specialist. According to the CV risk class, every patient should be followed up during cancer treatment to monitor any possible CV complications. Adequate control of AH related to antineoplastic treatments is crucial to prevent severe CVAEs. In the presence of high-profile risk or lack of response to anti-hypertensive therapy, the patients should be managed with a cardiovascular-oncology expert center.

Keywords: cardio-oncology; arterial hypertension; cardiovascular adverse event; cardiovascular prevention; cardiotoxic treatments

1. Introduction

Arterial hypertension (AH) is one of the most important cardiovascular (CV) risk factors and its prevalence has increased in past decades due to the aging of the population. At the same time, cancer has become one of the leading causes of death and several

oncologic drugs have been approved to improve the prognosis of these patients [1]. Patients with cancer have an increased risk of experiencing cardiovascular adverse events (CVAEs) while receiving potentially cardiotoxic oncologic treatment [2]. This probability is further increased in the presence of uncontrolled, concomitant AH (chronic or related to oncologic drugs). It is known that cancer therapy using old as well as new drugs may cause AH through different mechanisms and sometimes the increase in blood pressure (BP) may be responsible for chemotherapy withdrawal. More than 10 oncological class treatments have been identified as related to AH and CVAEs (Table 1) [3–12].

Table 1. Principle class of cancer treatments related to arterial hypertension.

	Drug Class	Main Molecules	Renal Damage	Cardiac Damage	Cardiovascular Toxicity
Anti-neoplastic	Anti-angiogenic	Bevacizumab (mAb against VEGF) Sunitinib (VEGF-R inhibitor)	Yes, proteinuria	Yes, Myocardial ischemia	- Rarefaction of capillaries - Increased arterial stiffness - Endothelial dysfunction due to NO reduction
	Proteasome inhibitor	Bortezomib Carfilzomib	Yes	Yes, heart failure, arrhythmias, myocardial ischemia	- Endothelial dysfunction - Vasoconstriction
	Anti-androgen	Abiraterone Enzalutamide	No	Yes	- Increase of ACTH and aldosterone levels
	Alkylating agent	Cisplatin Cyclophosphamide	Yes, tubular necrosis	Yes	- Endothelial and renal dysfunction -Vasoconstriction
	Vinca alkaloid	Vinblastine Vincristine	No	Yes	- Inhibition of endothelial cell proliferation
	Taxane	Paclitaxel Docetaxel	No	Yes, arrhythmias, LV dysfunction	- Inhibition of endothelial cell proliferation
	Anti-metabolite	Gemcitabine	Yes	Yes, myocardial ischemia	- Endothelial dysfunction - Oxidative stress
	HER-2 targeted	Trastuzumab	Yes, glomerulo-nephritis	Yes, LV disfunction	- Sympathetic activity - Vasoconstriction
	Anthracycline	Doxorubicin Daunorubicin	No	Yes, LV disfunction	- Endothelial dysfunction - Oxidative stress
	PI3K inhibitor	Copansilib	No	No	- Vasoconstriction
Non anti-neoplastic	Hormone	Corticosteroids	No	No	- Fluid retention - Vasoconstriction
	Immunomodulant	Ciclosporin A Tacrolimus INFα	Yes/No	No	- Sympathetic activity - Fluid retention - RAAS activity
	Erythropoietin	Endogenous Exogenous	No	No	- Blood viscosity - Vasoconstriction
	NSAID	Ibuprofen Ketoprofen	Yes	No	- Fluid retention - Prostacyclin reduction

mAb: monoclonal antibody, NO: nitric oxide, CAD: coronary artery disease, LV: left ventricular, PI3K: phosphoinositide-3 kinase, RAAS: renin-angiotensin-aldosterone system, NSAID: non-steroidal anti-inflammatory drugs.

In order to prevent the occurrence of AH and CVAEs during oncologic therapy or to administer a proper antihypertensive treatment if required, every patient with clinical indication of potentially cardiotoxic treatment should be evaluated for CV risk factors [13–17]. Despite the evidence of several cardiotoxic effects due to cancer therapies, guidelines on the assessment of cardiac status in cancer patients are still lacking. As a consequence, oncologists may face difficulties in evaluating CV risk, giving appropriate antihypertensive therapy and preventing CV complications. With this document, we propose a useful and practical guide, easily applicable in different clinical settings, that, with a simple scoring system, could aid oncologists and general practitioners in the cardiovascular risk stratification of every patient. We aimed to provide recommendations to support health professionals in selecting the best management strategy for patients, considering the impact on outcomes and the risk–benefit ratio of diagnostic and therapeutic tools.

2. Cardiovascular Risk Stratification

An efficient management of AH related to oncological treatments is crucial in order to prevent severe CVAEs and BP rises that could lead to premature discontinuation of chemotherapy. It is estimated that $1/3$ of cancer patients are affected by AH, making this condition the most common CV comorbidity in this population [4,18]. These data might be related to the fact that both AH and cancer are common with advanced age. In addition, the impact of cancer treatment, especially VEGF inhibitors and proteasome inhibitors (PI), has a fundamental role in BP rise. AH is an important CV risk factor and should be managed following the current guidelines: both the ESH/ESC Guidelines for the management of arterial hypertension [13] and the ESC recommendations on management of cancer treatments and cardiovascular toxicity [19] underline the relevance of CV risk factor evaluation in order to define the profile risk of every patient.

The rationale of the CV risk stratification is: prevention, early diagnosis and treatment of CV complications related to oncologic treatments, reduction of therapy discontinuation due to CVAEs and optimization of cardiovascular therapy.

2.1. The Workup of Cardiovascular Risk Stratification

The process of risk stratification is divided into three phases:

(1) Baseline evaluation (preliminary phase): identification of CV risk factors before cancer treatment initiation in order to establish the probability of developing CVAEs, to eliminate the removable risk factors and optimize CV therapy;
(2) Ongoing evaluation (active phase): early diagnosis and treatment of conditions related to cardiovascular toxicity during oncologic treatment;
(3) Long-term evaluation (tardive phase): to diagnose and treat tardive cardiovascular toxicity.

In every phase, the collegial evaluation between oncologists and cardiovascular specialists to assess the possibility to continue, modify or discontinue the cancer therapy is fundamental.

2.2. The Scoring System

Patients with known AH should be stratified as low, moderate, high or very high CV risk based on blood pressure levels, concomitant CV risk factors and organ damage. Non-hypertensive patients with clinical indication of anti-VEGF drugs or other potentially cardiotoxic therapies should be stratified for CV risk as well. The European guidelines on prevention of CV disease recommend the use of the "Systematic COronaric Risk Score" (SCORE) [20], updated in 2019 [21]. This score system estimates the risk of a first atherosclerotic fatal event at 10 years, considering five parameters: age, gender, smoking, cholesterol levels and BP values [22].

In presence of diagnosed CV disease such as diabetes mellitus (DM) type 1 or 2, elevated individual CV risk factors (AH grade 3 included) or chronic renal disease (grade 3–5), patients should be automatically included in the high (CV mortality 5–10%) or very

high CV risk class (CV mortality > 10% at 10 years). In these patients the SCORE system should not be applied.

During the baseline evaluation, cancer patients with clinical indication of potentially cardiovascular toxic therapy should be divided into two main groups (based on ESC/EAS guidelines 2019) [21]:

(1) High CV risk (Table 2), which includes patients:

(a) With high or very high CV risk: Patients with known organ damage or high probability to develop organ damage in presence of multiple risk factors or predisposing diseases (diabetes mellitus, chronic renal insufficiency > 3 grade). These patients should be categorized at high risk to develop CV complications (such as stroke, myocardial infarction, heart failure, renal insufficiency and peripheral vasculopathy) induced by AH related to the oncologic treatment.

(b) Previously treated with cardiovascular toxic therapy (high risk of iatrogenic AH): Patients previously treated with anthracyclines or other potentially cardiotoxic drugs, past chest radiotherapy, with ejection fraction reduction during previous cancer treatments, AH or CVAEs occurrence during prior therapies.

Both patients affected by known cardiopathy, vascular disease or with a SCORE risk >5% should be evaluated by a specialist in order to define the severity of the known CV disease and reveal and define the unknown organ damage (that has a high probability to be found in the presence of multiple risk factors). Similarly, patients previously treated with cardiotoxic therapy should be evaluated by a specialist in order to define the severity of organ damage.

(2) Moderate or low CV risk (Table 2), in which patients could be divided into:

(a) With known AH: if the baseline evaluation does not reveal uncontrolled AH or subclinical organ damage, only first level diagnostic exams and routine BP monitoring should be performed in order to avoid development of AH in patients treated with VEGF inhibitors and PI. In presence of uncontrolled AH or suspected/evident subclinical organ damage at the baseline workup, second level investigations will be necessary to better define the organ damage and optimize the antihypertensive therapy.

(b) Without known AH: similarly to the previous subgroup, if no AH or organ damage was revealed, only first level exams are required. On the other hand, in the presence of subclinical organ damage, a deeper specialist investigation is recommended through an ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM). This would be aimed to detect masked AH and treat accordingly. Additionally, strict BP monitoring and echocardiography are indicated to define the potential cardiac damage.

The oncologists should independently manage the moderate/low CV risk patients, evaluating on a case-by-case basis if a specialist consultation is required (second level examination by a cardiologist or hypertension specialist).

Table 2. Checklist for CV risk scoring for cancer patients with indications of cardiotoxic treatment.

Anamnestic Assessment	YES?		
Previous myocardial infarction	☐	**Very high risk**	**Referral to the cardiologist/ hypertension specialist**
Coronary or other arterial revascularization procedures	☐		
Acute coronary syndrome or other arterial atherosclerotic occlusions	☐		
Previous stroke or transient ischemic attack	☐		
Aorta aneurysm	☐		
Peripheral artery disease	☐		
Diabetes mellitus: with *organ damage* [a]	☐		
with *other major risk factor*: - uncontrolled BP (grade 3) - severe dyslipidemia - smoke	☐		
Severe CKD (GFR < 30 mL/min/1.73 mq)	☐		
SCORE ≥ 10%	☐		
Markedly elevated single risk factor: - Uncontrolled BP (grade 3) - Severe dyslipidemia (col tot >310 mg/dL) - Familiar dyslipidemia - Smoke	☐	**High risk**	**Referral to the cardiologist/ hypertension specialist**
Diabetes Mellitus - without *organ damage* [a] - duration ≥10 years - with an additional risk factor	☐		
Moderate CKD (GFR 30–59 mL/min/1.73 mq)	☐		
SCORE ≥5 and <10%	☐		
TT echocardiogram: - Left ventricular hypertrophy (LVMi > 95 g/mq o ≥115 g/mq F/M); - GLS > −18% - EF < 52/54% M/F or alteration in regional/segmental contractility	☐		
Uncontrolled resistant arterial hypertension (3 drugs included 1 diuretic at the full dose)	☐		
Young patients with DM: - DM type 1 < 35 years; - DM type 2 < 50 years; - DM duration < 10 years; - without additional risk factors	☐	**Moderate risk**	**Oncologist/GP care**
SCORE ≥1% and <5% at 10 years	☐		
SCORE <1%	☐	**Low risk**	**Oncologist/GP care**

Modified from "2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk" [21]. [a] proteinuria, neuropathy. BP: blood pressure, CKD: chronic kidney disease, GFR: glomerular filtration rate, LVMi: left ventricular mass indexed for BSA, GLS: global longitudinal strain, EF: ejection fraction, DM: diabetes mellitus, GP: general practitioner, TT: transthoracic.

2.3. Cardiovascular Risk Stratification: Different Approach between Genders

Chemotherapies have improved the survival rates of cancer patients but, at the same time, has increased related cardiovascular toxicity. During CV risk stratification, the different CV effects of chemotherapy on men and women should be considered. Breast cancer chemotherapy (such as anthracycline or HER2-targeted drugs) and radiotherapy [23] may increase the risk of CVAEs in women. Recent data [24] demonstrated that the average lifetime risk of developing CV disease in women at 50 years of age is on average 40% and this percentage rises as the number of risk factors increases. Premenopausal women are relatively protected against CV disease, compared with age-matched men, but the protective effect decreases after menopause. The identification and the treatment of CV risk factors is necessary to reduce the occurrence of CVAEs. The common CV risk factors affect both genders with different relative importance: women with DM type 2, dyslipidemia or with a cigarette consumption more than 20/day have a higher risk of fatal coronary artery disease compared with men; obesity and inactivity have higher prevalence in women; women

develop AH later than men; but, elderly women have higher AH prevalence than elderly men. In addition, there are a number of risk factors unique to women, such as: polycystic ovary syndrome, preterm delivery, hypertensive pregnancy disorders, gestational DM and menopausal transition (surgical or spontaneous) [13,24,25]. The identification of the CV risk factors unique to woman during reproductive years may improve the current risk assessment strategies. Moreover, it should be considered that some CV diseases are more prevalent in women, such as spontaneous coronary artery dissection, stress-induced cardiomyopathy, atypical myocardial infarction presentations [26] and heart failure with preserved EF.

For these reasons, the assessment of CV risk should consider the relative importance of the common CV risk factors for men and women, the effects of the risk factors unique to women and the different prevalence and presentation of CV diseases between genders.

3. Baseline Cardiovascular Evaluation

The assessment of cardiovascular risk before beginning a potentially cardiotoxic oncologic therapy is fundamental in order to establish the probability of experiencing CVAEs and, on this basis, start proper management, considering the impact on outcomes and the risk–benefit ratio of diagnostic and therapeutic tools.

3.1. First Level Evaluation

The first level baseline evaluation is done under the competence of an oncology specialist and includes:

- Patient history: to identify major CV risk factors (age, gender, smoking habits, DM, AH and dyslipidemia), pre-existing CV disease or sign/symptoms suggestive of a specific unrecognized CV disease;
- Evaluation of the assumed anti-hypertensive or cardiologic therapy;
- Complete physical examination comprehensive of BP measurements (as recommended in ESH/ESC guidelines 2018) [13];
- SCORE risk calculation;

To complete the first level evaluation the oncologist has to evaluate the results of the subsequent tests:

- Routine blood tests (blood cell count, creatinine, electrolytes, glycemia, uric acid, hepatic profile) along with protein electrophoresis, urine exam, microalbuminuria, TSH reflex, HbA1c, lipid and martial profile, dosage of natriuretic peptides;
- Electrocardiogram;
- Transthoracic echocardiogram, if possible, with global longitudinal strain (GLS) assessment [27];
- ABPM and HBPM.

3.2. Second Level Evaluation

The second level evaluation is competence of the cardiologist/cardio-oncologist/hypertensive specialist. Patients with high or very high CV risk or those previously treated with cardiotoxic therapies require a second level evaluation. In the presence of moderate CV risk or abnormalities on first level investigations, the need for a second level examination should be evaluated on an individual basis.

The second level evaluation is composed of:

- Cardio-oncological assessment with transthoracic echocardiogram (including GLS assessment);
- If appropriate, according to clinical judgement: stress echocardiography, treadmill test, TSA and lower limb artery Doppler, coronary CT and cardiac MR;
- Abdomen US scan in presence of altered renal function or proteinuria/microalbuminuria. If appropriate, perform a nephrological evaluation;

- ABPM in presence of organ damage in patient with unknown AH in order to detect masked AH, or to optimize the antihypertensive therapy in case of uncontrolled AH;
- Other specialist examinations for specific diseases identified in the first screening.

4. Diagnosis and Treatment of Arterial Hypertension

Guidelines on treatment of AH in cancer patients receiving potentially cardiotoxic therapies are still lacking. Therefore, the following recommendations will concern AH treatment in general, with a subsequent focus on the characteristics of the subgroup with AH related to specific cancer treatment.

4.1. Arterial Hypertension Diagnosis

Arterial hypertension is defined as office systolic BP $\geq$ 140 mmHg or office diastolic BP $\geq$ 90 mmHg at least in two measurements a few days apart [28].

Patients with cancer and clinical indication of potentially cardiotoxic oncologic treatment should have two BP measurements (about 2 weeks apart) to verify BP levels, either spontaneous or on antihypertensive therapy. Office BP measurements should be performed in a quiet room in a sitting position, at least two measurements 15–30 s apart at the non-dominant arm (usually the left arm). The utilized device if automated should be validated.

The type of measuring could affect both the diagnosis and the follow-up of the patients. For this reason, it is fundamental to understand the difference between "office" (assessed in the medical office) and "out-of-office".

4.2. Out-of-Office BP to Reveal White Coat and Masked Hypertension

Out-of-office BP could be measured through the ABPM or at home with the help of validated automated devices. The measured office BP values should be confirmed outside the medical setting. Therefore, ABPM and HBPM assessments are useful for confirmation of AH diagnosis, or in case of discrepancies between office and out-of-office BP values for the identification of isolated clinical AH (or white coat AH) and masked hypertension. Increased office BP values and normotension on ABPM/HBPM identifies the clinical isolated AH. On the other hand, increased BP on ABPM/HBPM with normotensive values on office evaluation defines the condition of masked AH [17,29].

Therefore, the diagnosis of AH in a previously normotensive patient requires a combined evaluation of office and out-of-office BP assessment. The evaluation of HBPM in hypertensive patients on treatment is fundamental in order to verify the efficacy of antihypertensive treatment. In the same way, in cancer patients receiving potentially cardiotoxic treatments, HBPM allows health professionals to verify the control of BP during the days leading up to oncologic therapy and empowers the patients to verify potential BP increases in the days after chemotherapy infusions.

ABPM-24h is the best method of BP measuring that correlates with organ damage and CVAEs related to hypertension [13,29]. In cancer patients with moderate and low CV risk, the ABPM should be required by the oncologists (Table 3).

4.3. When to Begin the Antihypertensive Treatment?

The decision to begin an antihypertensive treatment should consider a global approach of CV risk stratification. The patient will be allocated in a CV risk class considering more CV risk factors and not only the simple office BP value. Patients with indication of cardiotoxic therapies should have controlled BP values, with a security office BP value < 140/90 mmHg and controlled ABPM and HBPM values.

The European guidelines of AH propose aggressive targets for many patient categories [13]: the lack of evidence about cancer patients should suggest caution in reducing BP values. Clinicians should prescribe an antihypertensive treatment in order to allow the oncologic therapy continuation in a safe condition.

Table 3. Interpretation of ABPM exam [30].

Quality	At least 22 h of measurements and almost 1 measurement every 20 min in the day and 1 every 30 min in the night.
Interpretation	Compare systolic and diastolic BP mean values during the 24 h, the day-time and the night-time with the normal ranges: SBP and/or DBP Mean day BP value 135 85 Mean night BP value (during sleep) 120 70 Mean 24 h BP value 130 80 Home BP value 135 85
	Evaluate the night BP dipping: Normal: 10% Absent < 10% Inverted Absent and inverted dipping are pathological conditions in the presence of normal sleep quality.
	Night-time BP value standard deviation analysis: if > 11 mmHg, possible major impact of BP rise on organ damage.
	Correlation between BP values and possible reported symptoms.

ABPM: ambulatory blood pressure monitoring, BP blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure.

4.4. Which Treatment?

Five drug classes have a major recommendation for AH treatment: ACE inhibitors (ACEi), angiotensin II receptor blockers (ARB), beta-blockers (BB), calcium channel blockers (CCB) and diuretics. For mechanism of action and possible collateral effects of these classes of drugs, please refer to the European guidelines of arterial hypertension [13].

Antihypertensive therapy indications for oncologists:

Patients affected by cancer in accordance with their CV profile risk should be treated firstly with CCB and/or ACEi/ARB. In case of lack of efficacy, the antihypertensive treatment could be optimized with the association of BB and/or thiazide or thiazide-like diuretics (Figure 1).

Antihypertensive therapy indications for hypertension specialists/cardiologists:

Patients with uncontrolled AH in the presence of the above-mentioned antihypertensive therapies (full dose) define the category of resistant arterial hypertension (RAH). In this case, the patients should be referred to a cardiologist/hypertension specialist in order to revise the antihypertensive treatment considering the anamnestic profile, the characteristics of the ongoing treatment and the current evidence.

The key elements of the treatments are (Table 4):

- Eliminate possible factors/substances which could reduce the BP control;
- Identify and modify incorrect habits (obesity, scarce physical activity, alcohol assumption, high salt or low fiber diet);
- Optimization of the ongoing antihypertensive therapy (synergic drug activity);
- Consider secondary causes of AH.

Consensus Document

Approach to Arterial Hypertension Therapy in patients treated with vasculo-toxic therapy

BP Levels

Office

<140/90   **Confirmed with**

Home or ABPM   yes →   **Stop**
At TARGET

no ↓

C **Calcium channel blockers**

i.e.
Amlodipine (5-10 mg)   Power
Felodipine (5-10 mg)   Side effects
Manidipine (10-20 mg)

and/or

Side effects: tachycardia, peripheral edema

ACE-I
i.e. Ramipril (2.5-10 mg)

A **RAAS inhibitors**

Angiotensin II Receptorc blockers (ARB)
i.e. Telmisartan (20-80 mg)

eventually
associated to

Side effect: cough   Warning: GFR<30 cc/m

Check creatinine, Na+, K+

i.e.
Nebivolol (at increased dosage 2.5 mg to 5 mg
after 15 days)

B **Beta blockers**

Side effects.: bradycardia

Controindications: bradycardia, asthma

Caution should be used for:
Diuretics electrolytes disturbance.
Verapamil and Diltiazem inhibit Cyt P3A4 (may increase levels of sunitinib) and increase PR interval.
Caution should be used when associated with drugs that can prolong QT.
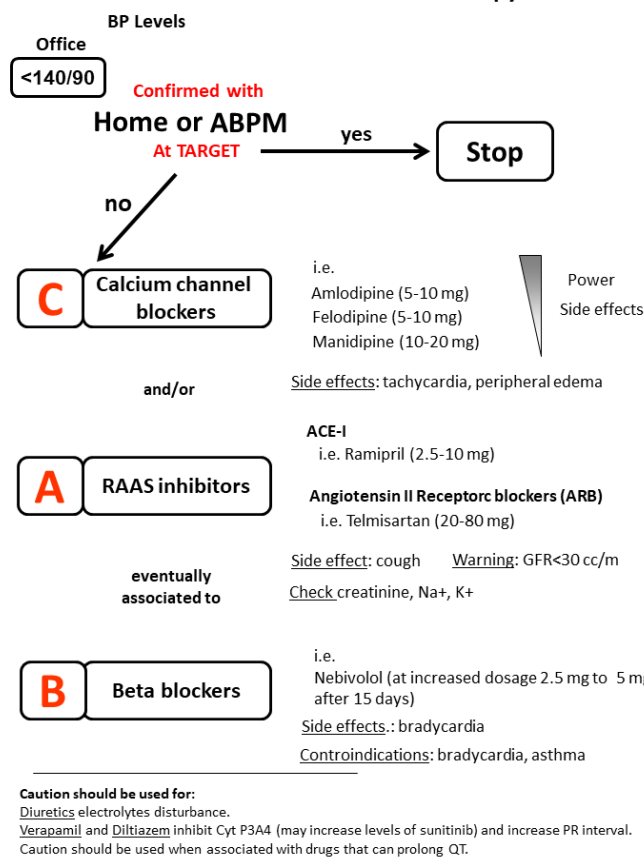
Figure 1. Approach to arterial hypertension therapy in patients treated with cardiovascular toxic therapy. BP: blood pressure, ABPM: ambulatory blood pressure monitoring, ACEi: angiotensin converting enzyme inhibitors, RAAS: renin-angiotensin-aldosterone system.

Table 4. Principles of evaluation of patients with resistant arterial hypertension.

Patient History:
- AH duration;
- HBPM;
- Family history of CV events;
- Habits (alcohol, smoking, recreational drug use, i.e., cocaine);
- Licorice or herbal products abuse;
- Lifestyle (physical inactivity, stress);
- Sleep disturbances (e.g., OSA);
- Drugs (antihypertensive drugs, NSAIDs, corticosteroids, collateral effects/intolerance).
Physical examination:
- Signs of secondary hypertension (hump, fat distribution, hypertrophic lower limb muscles, neck circumference, cutaneous sweating).
Laboratory tests:
- Creatinine, urea, electrolytes, glycemia, HbA1c, uric acid, TSH reflex, lipid profile, urine exam;
- 24 h diuresis: quantification of fluid in-take, sodiuria, creatininuria, creatinine clearance, metanephrines dosage, urinary free cortisol;
- Serum hormones: aldosterone levels, PRA.
Instrumental analysis:
- Transthoracic echocardiogram (with GLS assessment for subclinical/clinical damage);
- ABPM;
- Renal artery color-Doppler (or renal scintigraphy/CT/MR/arteriography based on the center's expertise);
- Polysomnography.

AH: arterial hypertension; HBPM: home blood pressure monitoring; CV: cardiovascular; OSA: obstructive sleep apnea; NSAID: non-steroidal anti-inflammatory drugs; PRA: plasma renin activity.

5. Follow-Up

Patients suffering from cancer with clinical indication of cardiotoxic therapies should be re-evaluated periodically (office BP value measurements, ECG, TT echocardiogram with GLS assessment) by the oncologist. Patients eligible for cardiologic/hypertension specialist care should be evaluated at the baseline (before beginning therapy) and after 6 months. Subsequently, if the clinical–therapeutic approach is effective, they could be managed by the oncologist for overall management. These patients must be re-evaluated by the hypertension specialist in case of uncontrolled BP values, CVAEs, development of left ventricular hypertrophy, ECG abnormalities or GLS reduction during therapy (Figure 2).
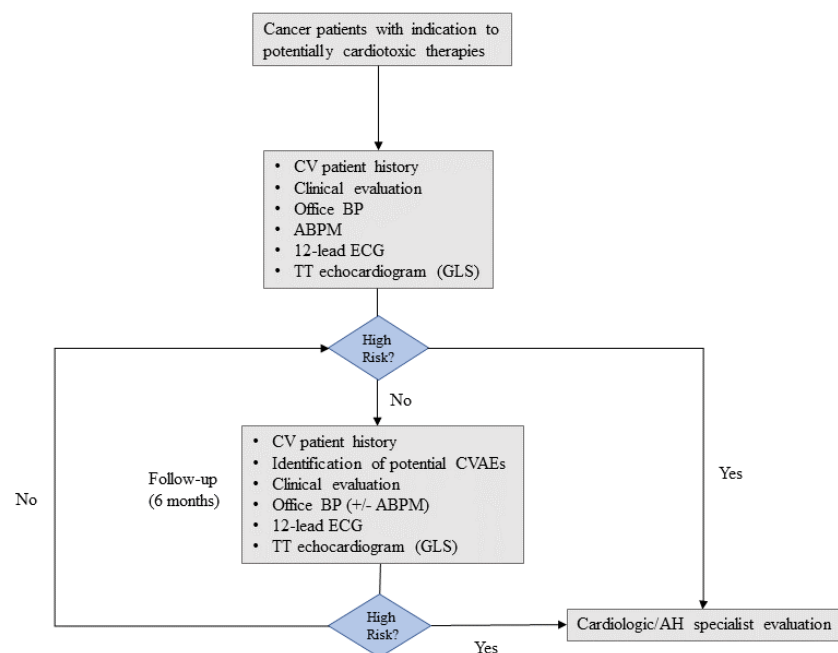
Figure 2. Protocol of patient selection and follow-up. CV: cardiovascular, BP: blood pressure, ABPM: ambulatory blood pressure monitoring, GLS: global longitudinal strain, CVAEs: cardiovascular adverse events; AH arterial hypertension, TT: transthoracic echocardiography.

6. Possible Adverse Cardiovascular Effects

When an adverse effect occurs (grade 3–4) [31], the possible relationship with the administered antineoplastic therapy should be investigated. In presence of a direct or indirect relationship with the chemotherapic agent, this must be interrupted, and the clinical case managed following the recommendation concerning the specific CV pathology (i.e., heart failure or atrial fibrillation). A therapy optimization with potential introduction of more specific antihypertensive drugs should be considered in case of AH (i.e., in presence of heart failure, introduce loop diuretics).

Other pathological conditions might be identified during specific treatments:

- *Proteinuria*: renal protein excretion >300 mg/24 h.

This is a frequent side effect of anti-VEGF drugs and is often associated with uncontrolled AH [32]. Significative proteinuria (>2 gr/24 h) could be a potential contraindication to continue the anti-VEGF therapy. In presence of a nephrosic proteinuria, the nephrologist support is mandatory for a correct therapeutic management. It is recommended to introduce ACEi/ARB therapy if not in use.

- *Hypotension*: SBP (systolic blood pressure) <90 mmHg.

From the data analysis of multiple myeloma patients treated with carfilzomib and followed by our specialized center (Hypertension Unit, Città della Salute e della Scienza, Turin), hypotension has been identified as a potential adverse effect observed

in a small but significative proportion of patients. This event could have many causes, so the clinicians must consider the following:

- Systemic: infections, volume depletions;
- Iatrogenic: over-treated AH;
- Dysautonomia: it is useful to verify clinostatic and orthostatic BP;
- Coronary spasm/occlusion: in the presence of high risk of coronary occlusion or symptoms/signs suggestive of coronary occlusion, this suspicion must be excluded or confirmed with specific tests.

- *Dyspnea*:

This is a frequent reported CV event during carfilzomib treatment [9,33,34]. According to the severity of the symptom it is necessary to exclude the cardiac causes. Initial evaluation should include an accurate clinical–anamnestic assessment in order to identify signs of heart failure, considering also the differential diagnosis with other non-cardiac causes of dyspnea. As first level examinations, ECG, chest X-ray, lung US, TT echocardiogram, serum NTproBNP, troponin T and D-dimer level should be performed.

7. Conclusions

AH is one of the most important CV risk factors and patients with cancer receiving a potentially cardiotoxic oncologic therapy have an increased risk of uncontrolled AH and CVAEs. Sometimes, the increase in BP may be responsible for chemotherapy withdrawal. Despite the evidence of several cardiovascular toxic effects due to cancer therapies, guidelines on the assessment of cardiac status in cancer patients are still lacking. For this reason, an expert panel of oncology networks from Piedmont and Aosta Valley (North-Western Italy) have proposed an easy CV scoring system based on the European Guidelines on cardiovascular disease prevention [20]. According to the CV risk class assigned, an appropriate follow-up is also suggested: patients with low/moderate risk could be entirely evaluated and followed by oncologists and, instead, patients with high/very high risk should be managed with cardiovascular/oncology expert specialists.

References

1. Kidoguchi, S.; Sugano, N.; Tokudome, G.; Yokoo, T.; Yano, Y.; Hatake, K.; Nishiyama, A. New Concept of Onco-Hypertension and Future Perspectives. *Hypertension* **2020**, *77*, 1–12. [CrossRef]
2. Katsi, V.; Magkas, N.; Georgiopoulos, G.; Athanasiadi, E.; Virdis, A.; Masi, S.; Kliridis, P.; Hatziyanni, A.; Tsioufis, C.; Tousoulis, D. Arterial Hypertension in Patients under Antineoplastic Therapy: A Systematic Review. *J. Hypertens.* **2019**, *37*, 884–901. [CrossRef] [PubMed]
3. Milan, A.; Puglisi, E.; Ferrari, L.; Bruno, G.; Losano, I.; Veglio, F. Arterial Hypertension and Cancer. *Int. J. Cancer* **2014**, *134*, 2269–2277. [CrossRef] [PubMed]
4. Tini, G.; Sarocchi, M.; Tocci, G.; Arboscello, E.; Ghigliotti, G.; Novo, G.; Brunelli, C.; Lenihan, D.; Volpe, M.; Spallarossa, P. Arterial Hypertension in Cancer: The Elephant in the Room. *Int. J. Cardiol.* **2019**, *281*, 133–139. [CrossRef] [PubMed]

5. Abi Aad, S.; Pierce, M.; Barmaimon, G.; Farhat, F.S.; Benjo, A.; Mouhayar, E. Hypertension Induced by Chemotherapeutic and Immunosuppresive Agents: A New Challenge. *Crit. Rev. Oncol. Hematol.* **2015**, *93*, 28–35. [CrossRef]

6. Soultati, A.; Mountzios, G.; Avgerinou, C.; Papaxoinis, G.; Pectasides, D.; Dimopoulos, M.A.; Papadimitriou, C. Endothelial Vascular Toxicity from Chemotherapeutic Agents: Preclinical Evidence and Clinical Implications. *Cancer Treat. Rev.* **2012**, *38*, 473–483. [CrossRef]

7. Herrmann, J.; Yang, E.H.; Iliescu, C.A.; Cilingiroglu, M.; Charitakis, K.; Hakeem, A.; Toutouzas, K.; Leesar, M.A.; Grines, C.L.; Marmagkiolis, K. Vascular Toxicities of Cancer Therapies: The Old and the New—An Evolving Avenue. *Circulation* **2016**, *133*, 1272–1289. [CrossRef]

8. Plummer, C.; Michael, A.; Shaikh, G.; Stewart, M.; Buckley, L.; Miles, T.; Ograbek, A.; McCormack, T. Expert Recommendations on the Management of Hypertension in Patients with Ovarian and Cervical Cancer Receiving Bevacizumab in the UK. *Br. J. Cancer* **2019**, *121*, 109–116. [CrossRef]

9. Bruno, G.; Bringhen, S.; Maffei, I.; Iannaccone, A.; Crea, T.; Ravera, A.; Astarita, A.; Vallelonga, F.; Salvini, M.; Gay, F.; et al. Cardiovascular Organ Damage and Blood Pressure Levels Predict Adverse Events in Multiple Myeloma Patients Undergoing Carfilzomib Therapy. *Cancers* **2019**, *11*, 622. [CrossRef]

10. Bringhen, S.; De Wit, E.; Dimopoulos, M.A. New Agents in Multiple Myeloma: An Examination of Safety Profiles. *Clin. Lymphoma Myeloma Leuk.* **2017**, *17*, 391–407.e5. [CrossRef]

11. Pagan, J.; Seto, T.; Pagano, M.; Cittadini, A. Role of the Ubiquitin Proteasome System in the Heart. *Circ. Res.* **2013**, *112*, 1046–1058. [CrossRef] [PubMed]

12. Versmissen, J.; Mirabito Colafella, K.M.; Koolen, S.L.W.; Danser, A.H.J. Vascular Cardio-Oncology: Vascular Endothelial Growth Factor Inhibitors and Hypertension. *Cardiovasc. Res.* **2019**, *115*, 904–914. [CrossRef] [PubMed]

13. Williams, B.; Mancia, G.; Spiering, W.; Rosei, E.A.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; De Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH Guidelines for Themanagement of Arterial Hypertension. *Eur. Heart J.* **2018**, *39*, 3021–3104. [CrossRef] [PubMed]

14. Milan, A.; Bruno, G.; Maffei, I.; Iannaccone, A.; Ravera, A.; Schiavone, D.; Veglio, F. Arterial Hypertension and Multiple Myeloma: Physiopathology and Cardiovascular Risk and 'Practical' Indications in Patients Receiving Carfilzomib. *Curr. Hypertens. Rev.* **2018**, *15*, 47–53. [CrossRef] [PubMed]

15. Curigliano, G.; Lenihan, D.; Fradley, M.; Ganatra, S.; Barac, A.; Blaes, A.; Herrmann, J.; Porter, C.; Lyon, A.R.; Lancellotti, P.; et al. Management of Cardiac Disease in Cancer Patients throughout Oncological Treatment: ESMO Consensus Recommendations. *Ann. Oncol.* **2020**, *31*, 171–190. [CrossRef]

16. Lyon, A.R.; Dent, S.; Stanway, S.; Earl, H.; Brezden-Masley, C.; Cohen-Solal, A.; Tocchetti, C.G.; Moslehi, J.; Groarke, J.D.; Bergler-Klein, J.; et al. Baseline Cardiovascular Risk Assessment in Cancer Patients Scheduled to Receive Cardiotoxic Cancer Therapies: A Position Statement and New Risk Assessment Tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society. *Eur. J. Heart Fail.* **2020**. [CrossRef]

17. Cohen, J.B.; Geara, A.S.; Hogan, J.J.; Townsend, R.R. Hypertension in Cancer Patients and Survivors. *JACC CardioOncology* **2019**, *1*, 238–251. [CrossRef]

18. Bringhen, S.; Milan, A.; D'Agostino, M.; Ferri, C.; Wäsch, R.; Gay, F.; Larocca, A.; Offidani, M.; Zweegman, S.; Terpos, E.; et al. Prevention, Monitoring and Treatment of Cardiovascular Adverse Events in Myeloma Patients Receiving Carfilzomib A Consensus Paper by the European Myeloma Network and the Italian Society of Arterial Hypertension. *J. Intern. Med.* **2019**, *286*, 63–74. [CrossRef]

19. Zamorano, J.L.; Lancellotti, P.; Rodriguez Muñoz, D.; Aboyans, V.; Asteggiano, R.; Galderisi, M.; Habib, G.; Lenihan, D.J.; Lip, G.Y.H.; Lyon, A.R.; et al. 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. [CrossRef]

20. Piepoli, M.F.; Hoes, A.W.; Agewall, S.; Albus, C.; Brotons, C.; Catapano, A.L.; Cooney, M.T.; Corrà, U.; Cosyns, B.; Deaton, C.; et al. 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. *Eur. Heart J.* **2016**, *37*, 2315–2381. [CrossRef]

21. Mach, F.; Baigent, C.; Catapano, A.L.; Koskinas, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; De Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk. *Eur. Heart J.* **2020**, *41*, 111–188. [CrossRef] [PubMed]

22. Heart Score ESCardio. Available online: https://Heartscore.Escardio.Org/2016/Quickcalculator.Aspx?Model=EuropeLow (accessed on 14 January 2021).

23. Darby, S.C.; Ewertz, M.; McGale, P.; Bennet, A.M.; Blom-Goldman, U.; Brønnum, D.; Correa, C.; Cutter, D.; Gagliardi, G.; Gigante, B.; et al. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *N. Engl. J. Med.* **2013**, *368*, 987–998. [CrossRef] [PubMed]

24. Garcia, M.; Mulvagh, S.L.; Merz, C.N.B.; Buring, J.E.; Manson, J.A.E. Cardiovascular Disease in Women: Clinical Perspectives. *Circ. Res.* **2016**, *118*, 1273–1293. [CrossRef] [PubMed]

25. Maffei, S.; Guiducci, L.; Cugusi, L.; Cadeddu, C.; Deidda, M.; Gallina, S.; Sciomer, S.; Gastaldelli, A.; Kaski, J.C. Women-Specific Predictors of Cardiovascular Disease Risk—New Paradigms. *Int. J. Cardiol.* **2019**, *286*, 190–197. [CrossRef] [PubMed]

26. Mehta, L.S.; Beckie, T.M.; DeVon, H.A.; Grines, C.L.; Krumholz, H.M.; Johnson, M.N.; Lindley, K.J.; Vaccarino, V.; Wang, T.Y.; Watson, K.E.; et al. Acute Myocardial Infarction in Women: A Scientific Statement from the American Heart Association. *Circulation* **2016**, *133*, 916–947. [CrossRef] [PubMed]

27. Čelutkienė, J.; Pudil, R.; López-Fernández, T.; Grapsa, J.; Nihoyannopoulos, P.; Bergler-Klein, J.; Cohen-Solal, A.; Farmakis, D.; Tocchetti, C.G.; Haehling, S.; et al. The Role of Cardiovascular Imaging in Cancer Patients Receiving Cardiotoxic Therapies: A Position Statement on Behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council Of. *Eur. J. Heart Fail.* **2020**. [CrossRef] [PubMed]
28. Unger, T.; Borghi, C.; Charchar, F.; Khan, N.A.; Poulter, N.R.; Prabhakaran, D.; Ramirez, A.; Schlaich, M.; Stergiou, G.S.; Tomaszewski, M.; et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* **2020**, *75*, 1334–1357. [CrossRef]
29. Cohen, J.B.; Cohen, D.L. Integrating Out-of-Office Blood Pressure in the Diagnosis and Management of Hypertension. *Curr. Cardiol. Rep.* **2016**, *18*, 112. [CrossRef]
30. Omboni, S.; Palatini, P.; Parati, G. Standards for Ambulatory Blood Pressure Monitoring Clinical Reporting in Daily Practice: Recommendations from the Italian Society of Hypertension. *Blood Press. Monit.* **2015**, *20*, 241–244. [CrossRef]
31. U.S. Department of Health and Human Services. Cancer Therapy Evaluation Program (CTEP): Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. 2007. Available online: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf (accessed on 14 January 2021).
32. Rosner, M.H.; Perazella, M.A. Acute Kidney Injury in Patients with Cancer. *N. Engl. J. Med.* **2017**, *376*, 1770–1781. [CrossRef]
33. Siegel, D.; Martin, T.; Nooka, A.; Harvey, R.D.; Vij, R.; Niesvizky, R.; Badros, A.Z.; Jagannath, S.; McCulloch, L.; Rajangam, K.; et al. Integrated Safety Profile of Single-Agent Carfilzomib: Experience from 526 Patients Enrolled in 4 Phase II Clinical Studies. *Haematologica* **2013**, *98*, 1753–1761. [CrossRef] [PubMed]
34. Franken, B.; van de Donk, N.W.C.J.; Cloos, J.C.; Zweegman, S.; Lokhorst, H.M. A Clinical Update on the Role of Carfilzomib in the Treatment of Relapsed or Refractory Multiple Myeloma. *Ther. Adv. Hematol.* **2016**, *7*, 330–344. [CrossRef] [PubMed]