

# Hypertension in Patients with Cancer as a Predictor of Ventricular Dysfunction

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Hypertension is the most prevalent comorbidity (38%) in patients with cancer and is considered an important modifiable risk factor for the development of cardiovascular events, including heart failure (HF). Importantly, hypertension may worsen the prognosis of patients with cancer and the severity of some types of cancer.<sup>1,2</sup> In addition, cancer treatments may aggravate pre-existing or even cause new hypertension,<sup>1,2</sup> making the role of this risk factor even more complex and multifaceted.

It is important to note that the use of cardiotoxic drugs in association with an important and prevalent cardiovascular risk factor such as hypertension makes HF a common final pathway of damage to the heart. The association between hypertension, especially if poorly controlled, and increased risk of chemotherapy-induced cardiomyopathy and HF<sup>1,3</sup> has been demonstrated since studies with doxorubicin in the 1970s. In a retrospective study involving patients with lymphoma undergoing doxorubicin chemotherapy, the drug was an independent predictor of HF development, even after adjusting for risk factors. In addition, among patients undergoing treatment, hypertension was strongly associated with the development of HF.<sup>4</sup> Thus, managing this complex interaction should be a priority for patients with cancer.

Cancer and hypertension are intertwined from shared pathophysiological mechanisms, such as inflammation and oxidative stress, to common risk factors including smoking, diabetes, and obesity.<sup>1</sup> Some anticancer therapies (ACT), adjuvant therapies, anxiety, and pain may directly contribute to the increase in hypertension incidence or indirectly mediate its development through adverse effects such as nephrotoxicity. Furthermore, different factors related to cancer treatment can act as confounders for the measurement of blood pressure (BP). Conversely, hypertension may be associated with increased incidence or worsening of some types of cancer, such as renal cell cancer. In a prospective cohort of 577,800 adults followed for 12 years, hypertension

was associated with higher cancer incidence in men and higher cancer mortality in men and women.<sup>1</sup>

Several classes of oncologic drugs have been associated with the development or exacerbation of hypertension, which is the most common serious adverse event in patients with cancer undergoing chemotherapy.<sup>5</sup> The increase in BP may occur in the first weeks of treatment and can be considered a predictor of therapeutic efficacy. Retrospective data suggest that at least one-third of patients develop hypertension during follow-up,<sup>6</sup> with renal, gastric, and ovarian cancer being more associated with moderate and severe hypertension. Considering that treatment is time-sensitive, ACT should be maintained and the use of antihypertensives should be optimized. BP normalization typically occurs after discontinuation of treatment, allowing de-escalation or even discontinuation of anti-hypertensive drugs.

Among drugs that can potentially contribute to the onset or worsening of hypertension are vascular endothelial growth factor (VEGF) inhibitors, some tyrosine kinase inhibitors (TKI), abiraterone, enzalutamide, etc. This association has been best described for VEGF inhibitors and TKI. In VEGF inhibitors, hypertension (which is observed in almost 50% of patients) results from a reduction in nitric oxide production and angiogenesis, leading to increased vascular resistance as well as fluid retention due to impaired natriuresis and endothelin-1-mediated vasoconstriction.<sup>7</sup> As for TKI, a meta-analysis showed a 3.8-fold greater risk of hypertension, in addition to a 1.7-fold greater risk of cardiac ischemia and a 2.5-fold greater risk of left ventricular dysfunction.<sup>3,7</sup> Adjuvant therapies, such as corticosteroids, erythropoietin, nonsteroidal anti-inflammatory drugs, and radiotherapy, may also contribute to hypertension development through different mechanisms. Therefore, careful monitoring is required when these therapies are part of the cancer treatment regimen.

Besides the rapid development of hypertension during the treatment, several ACT are associated with late hypertension, with a higher prevalence among survivors (which may exceed 70% at age 50,<sup>8</sup> with adjusted rates 2.6 times higher than expected). In addition, survivors are 1.6 times more likely to be prescribed antihypertensive drugs than siblings without a history of cancer.<sup>9</sup> In this complex scenario, out-of-office BP monitoring in patients with cancer diagnosed with hypertension is advised at the beginning of cancer and hypertension treatments, as well as after intensification of treatment. Factors such as pain, fear, and anxiety can interfere with the assessment, which is also influenced by clinical, oncological, and pharmacological variables.

## Keywords

Hypertension; Cancer; Heart Failure; Anticancer therapy; Anti- Antihypertensives; Prognostic Assessment

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The number of robust studies prospectively testing the influence of chemotherapy drugs on the efficacy of different classes of antihypertensive drugs is limited. In general, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and dihydropyridine calcium channel blockers are considered first-line drugs, as in hypertension in general. Adding a second agent is preferable to increasing the dose, reducing the incidence of adverse effects. In this case, diuretics and second-generation beta-blockers are good options.<sup>2,3</sup> Attention should be paid to avoid specific drug interactions, such as: a) prescription of nondihydropyridine calcium channel blockers during chemotherapy with VEGF inhibitors, due to inhibition of cytochrome P450 3A4;<sup>10</sup> b) possible bradycardia with the use of beta-blockers or nondihydropyridine calcium channel blockers together with TKI; c) increase in the concentration of P-glycoprotein inhibitor chemotherapy drugs by beta-blockers; d) increase in the concentration of angiotensin receptor blockers and calcium channel blockers by chemotherapy drugs that inhibit CYP2C9 and CYP3A4, among others.<sup>10,11</sup>

Due to the lack of clinical and laboratory evidence on optimal BP control in patients with hypertension and cancer, recommendations are divergent. The criteria used by oncologists for dose management or discontinuation of therapies are from the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0,<sup>10</sup> a descriptive terminology for gradually reporting adverse events.<sup>1,5</sup> However, we understand that, when treating hypertension, each case should be considered individually, taking into account the oncological context and the prognosis to guide the therapeutical approach. Given that patients with cancer require multidisciplinary care, the multidisciplinary team should work together to find the best strategy.

For better management of hypertension in patients with cancer, we suggest that cardiovascular risk stratification and optimization of treatment of underlying comorbidities be conducted from the first assessment. For the treatment of cancer-associated hypertension, nonpharmacological therapies should be initially considered, including low-sodium diet, regular physical activity, smoking cessation, weight control, and other changes in health determinants.<sup>3</sup> The pharmacological approach should follow recommendations described in international guidelines but should also be individualized according to the specificities of each patient (Figure 1). For example, in patients on VEGF inhibitors or with proteinuria, drugs that act on the renin-angiotensin system should be prioritized as first choice; in patients susceptible to diarrhea, diuretics should be avoided due to loss of electrolytes and the risk of dehydration.<sup>3</sup>

Personal aspects should always be considered, such as in patients on VEGF inhibitors, in whom systolic and diastolic BP may increase in the first weeks of treatment which is, in fact, more common in the first cycles. Therefore, daily home BP monitoring is recommended in the first cycle, after each increase of ACT dose, and then every 2-3 weeks.<sup>2,3</sup> BP increase in response to chemotherapy is an independent predictor of better treatment outcomes.

Therefore, chemotherapy should not be interrupted, and hypertension should be treated aiming at ideal BP targets. Thus, individualized decision-making should consider pharmacological aspects such as those previously described, as well as specific aspects of the disease, previous treatments, clinical conditions, and pre-existing risk factors.

In the setting of cancer treatment, the interaction between hypertension, whether pre-existing or related to chemotherapy, and the development of HF is equally complex. In nonhypertensive patients with a history of colorectal, stomach, or breast cancer, BP measurement during treatment was associated with HF incidence, with an almost 2-fold increased risk in patients with stage 2 cancer.<sup>12</sup> Prospective data demonstrated that the presence of hypertension in cancer survivors increases the relative risk of cardiac events, including HF (relative risk = 19.4), irrespective of the risk associated with ATC.<sup>12</sup> Despite the need for further studies for better management, baseline cardiovascular assessment and multidisciplinary teamwork are essential for prevention and treatment guided by HF guidelines.

In conclusion, patients with cancer require careful BP monitoring by health professionals throughout their treatment and after its completion, in addition to a more careful multidisciplinary follow-up from a cardiovascular perspective, with defined quality parameters and in accordance with guideline recommendations. Such strategies aim to reduce the risk of end-organ damage, with an impact on morbidity and mortality, especially HF.

## Author Contributions

Conception and design of the research, Acquisition of data and Analysis and interpretation of the data: Marcatti PTF, Peixoto TFLF; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Marcatti PTF, Peixoto TFLF, Nascimento BR.

## Potencial conflito de interesse

Não há conflito com o presente artigo.

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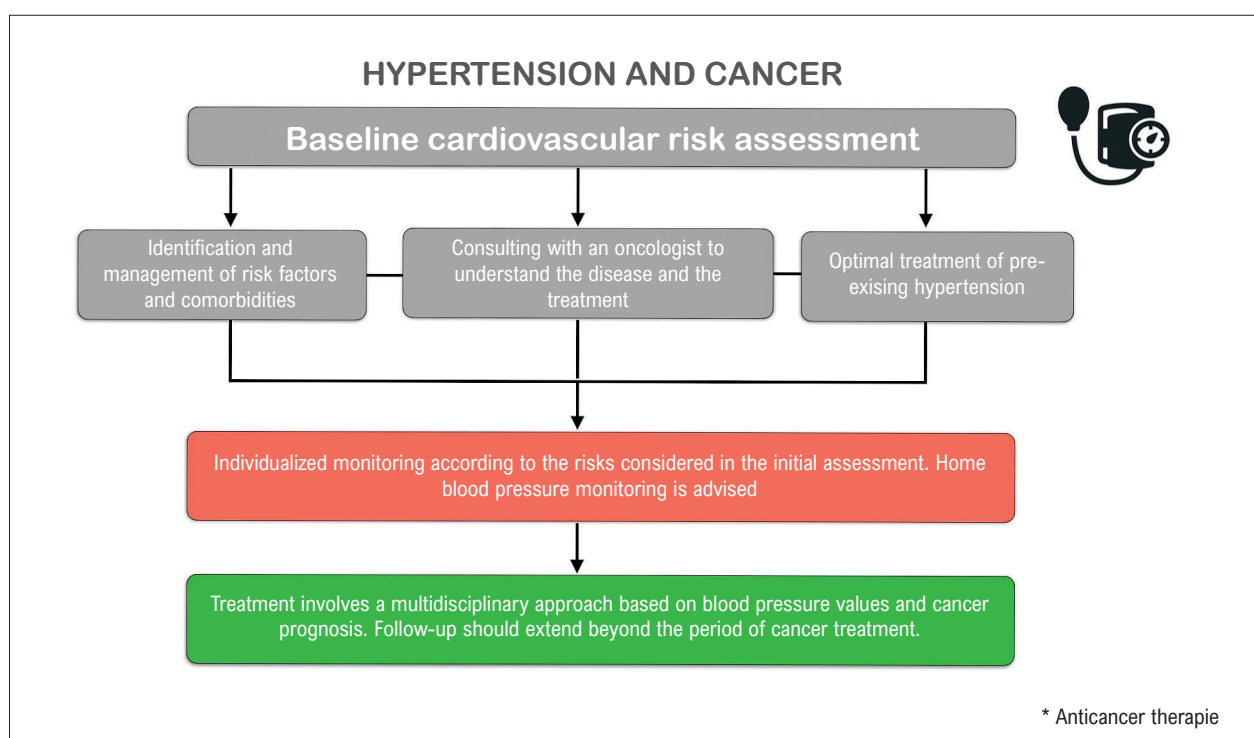
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## Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.



**Figure 1** – Flow diagram of recommendations for hypertension management in patients with cancer.

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