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HHS Public Access

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Hypertension. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

Hypertension. 2023 April ; 80(4): 685–710. doi:10.1161/HYPERTENSIONAHA.122.17947.

Established and Emerging Cancer Therapies and Cardiovascular System: focus on hypertension – mechanisms and mitigation

Lloyd E Butel-Simoes[*,1,2,4], **Tatt Jhong Haw**[*,2,3,4], **Trent Williams**[*,2,3,4], **Shanathan Sritharan**[5], **Payal Gadre**[5], **Sandra M Herrmann**[6], **Joerg Herrmann**[7], **Doan TM Ngo**[#,2,3,4], **Aaron L Sverdlov**[#,1,2,3,4]

[1]Cardiovascular Department, John Hunter Hospital, Newcastle, NSW, Australia

[2]College of Health and Medicine, University of Newcastle, NSW Australia

[3]Newcastle Centre of Excellence in Cardio-Oncology, NSW, Australia

[4]Hunter Medical Research Institute, New Lambton Heights, NSW Australia

[5]Department of Medicine, Hunter New England Local Health District, NSW, Australia

[6]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota

[7]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55902, USA

Abstract

Cardiovascular disease and cancer are two of the leading causes of death worldwide. While improvements in outcomes have been noted for both disease entities, the success of cancer therapies has come at the cost of at times very impactful adverse events such as cardiovascular events. Hypertension has been noted as both, a side effect as well as a risk factor for the cardiotoxicity of cancer therapies. Some of these dynamics are in keeping with the role of hypertension as a cardiovascular risk factor not only for heart failure, but also for the development of coronary and cerebrovascular disease, and kidney disease and its association with a higher morbidity and mortality overall. Other aspects, such as the molecular mechanisms underlying the amplification of acute and long-term cardiotoxicity risk of anthracyclines and increase in blood pressure with various cancer therapeutics remain to be elucidated. In this review, we cover the latest clinical data regarding the risk of hypertension across a spectrum of novel anti-cancer therapies as well as the underlying known or postulated pathophysiological mechanisms. Further, we review the acute and long-term implications for the amplification of the development cardiotoxicity with drugs not commonly associated with hypertension such as anthracyclines. An outline of management strategies, including pharmacological and lifestyle interventions as well as models of care aimed to facilitate early detection and more timely management of hypertension

Corresponding authors: Prof Doan TM Ngo, B.Pharm, PhD, FESC, FCSANZ, School of Biomedical Science and Pharmacy, College of Health, Medicine and Wellbeing, The University of Newcastle, NSW, Australia, T: +61 2 4033 9386, M: +61 (0) 413 822334, doan.ngo@newcastle.edu.au; **Prof Aaron L Sverdlov**, MBBS, PhD, FRACP, FCSANZ, FESC, FACC, School of Medicine and Public Health, College of Health, Medicine and Wellbeing, The University of Newcastle, NSW, Australia, T: +61 2 4042 0725, M: +61 (0) 478 113374, aaron.sverdlov@newcastle.edu.au.

*Drs LE Butel-Simoes, TJ Haw and T Williams are joint first authors on this manuscript

#Drs DTM Ngo and AL Sverdlov are co-senior and co-corresponding authors on this manuscript

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in cancer patients and survivors concludes this review, which overall aims to improve both cardiovascular and cancer-specific outcomes.

Keywords

Cardio-oncology; Hypertension; Cancer therapy; Epidemiology; Etiology; Mechanisms; Management

Introduction

There has been a rapid emergence of (next generation) anti-neoplastic treatments over the last few decades, which (combined with early detection strategies and population education) have markedly extended overall patient survival across almost all cancer types. Whilst the benefits of these therapies have been clearly established, the cardiovascular adverse events (CVAE) associated with these therapies have also emerged and can impact the quality of life and even the life expectancy of patients. The significance of this issue is magnified by the fact that cardiovascular disease (CVD) and cancer are the two most common causes of morbidity and mortality in developed nations.[1]

CVD and cancer not infrequently coexist, and mortality and morbidity from CVD is significantly higher amongst cancer patients.[2–4] The association is complex and not explained by one single (shared) risk factor such as age, smoking status, diabetes, alcohol intake, diet, obesity, chronic inflammatory states and genetic risk. Rather, it can be postulated that a combination of risk factors with pathophysiologic changes induced by cancer and its treatment generates an exaggerated risk.[5] One such factor is hypertension; in fact, numerous studies have confirmed hypertension to be a key factor for the risk of cardiac dysfunction and heart failure in patients exposed to anthracycline therapy.[6] Of further note, hypertension is not only a major risk factor for the development of CVAE, but can by itself be a form of CVAE. Indeed, multiple anti-cancer therapies have been linked to new onset or worsening hypertension (Table 1 and Figure 1).[7–10] This is on the background of an already ~20% higher prevalence of hypertension in cancer patients than in matched non-cancer control populations.[4]

Interest in this area among nephrologists, cardiologists, generalists, and oncologists has led to the emergence of “onco-hypertension” as a field within and beyond cardio-oncology and onco-nephrology. Onco-hypertension takes a broader approach to the understanding and management of hypertension, whilst acknowledging the gaps in evidence and the complexity of integrated factors including comorbidities, the choice of anti-cancer treatments, the cancer type, and patient factors.[11–13] Recent developments in this area include a harmonized definition for hypertension in cancer patients, which we will discuss herein. We will furthermore reflect on blood pressure surveillance and management strategies for patients undergoing cancer therapies, including new models of care such as remote monitoring. This review will also cover the role hypertension plays in the development of cardiotoxicity with drugs commonly not associated with hypertension as a side effect. This article will commence though with a summary of clinical data linking new and emerging anti-cancer

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treatments with hypertension and underlying established or putative mechanisms for this side effect profile.

VEGF Inhibitors

Vascular endothelial growth factor (VEGF) inhibitors are one of the classic targeted anti-cancer therapies, still in common use globally. VEGF-A is a potent angiogenesis growth factor, part of a VEGF family of ligands. VEGF's regulate angiogenesis via their effects on vascular endothelial cells affecting musculoskeletal growth, embryogenesis, reproductive function and importantly tumour genesis and growth.[14,15] VEGF-A has been the most effective target for anti-angiogenesis treatment primarily due to its overexpression across a vast range of solid tumour types, including colorectal cancer (CRC), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), peritoneal cancer, glioblastoma, cervical and ovarian cancers.[15,16]

Since approval of Bevacizumab, the first anti-VEGF-A recombinant humanised monoclonal antibody (mAb), there has been a steady growth of newer therapies within this class such as Ramucirumab, a VEGFR2 mAb, and Aflibercept, a novel fusion protein that has several targets (VEGF-A, VEGF-B, and PLGF),[15,17] now in use in advanced gastro-oesophageal adenocarcinomas, metastatic gastric cancer, NSCLC, CRC, and hepatocellular carcinoma.[17]

The success of these specific VEGF inhibitors (VEGFi) led to the development and use of targeted Tyrosine Kinase inhibitors (TKI) against VEGF receptors and other downstream pathways. The oral bioavailability of these small molecule therapies offered a significant benefit over first generation VEGFi whilst also providing significant downstream kinase pathway effects further enhancing anti-tumor effects. There is now an array of VEGFi's and VEGF-TKIs targeting a variety of downstream effector pathways available for treatment of many cancer types (Table 2).

Crucial role of VEGF signalling in vascular homeostasis, vascular neo-angiogenesis and the maintenance of endothelial cell function likely accounts for VEGF-inhibitor-related CVAE such as arterial thromboembolism, cardiac dysfunction, QT interval prolongation, arrythmia and most commonly hypertension.[18,19] There have also been reports of an increased risk of aneurysm and aortic dissection resulting from changes in the vascular wall which are compounded by the hypertensive effects of the treatment.[20] Many of the CVAE including hypertension have been demonstrated across both the extracellular VEGF-mAb and the intracellular VEGF-TKIs.[19]

Clinical and epidemiological evidence for VEGF inhibitor induced hypertension

Hypertension as a CVAE of VEGFi has been variably reported to range from 30% to 80% in both clinical trials and real world cohorts with a majority of patients experiencing some form of blood pressure increase (grade 1 or 2) generally occurring early, however the true incidence may be much higher given significant underreporting of low grade events.[19,21–23] More severe hypertension (grade 3 or 4) has been reported with the frequency of 6–40% in different clinical trials.[19]

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A meta-analysis from Totzeck *et al* included over 10 000 bevacizumab-treated patients across a variety of cancers demonstrated 4.73-fold relative risk increase of all-grade hypertension with bevacizumab treatment in a dose-dependent manner.[24] Comparatively in the most recent review of 105 RCTs with over 65000 cancer patients' treatment with VEGFi mAbs was associated with a 3.22-fold increased risk of all-grade hypertension and a 6.15-fold increased risk of high-grade hypertension. While individual VEGFi mAb types conferred differential hypertensive risk, factors such as cancer type, prior treatment and duration did not.[25]

Multiple systematic reviews, collectively including 100 VEGF-TKI RCTs, have also confirmed their significant hypertensive effects, with relative risk increase of all-grade hypertension of between 3.46 and 3.85 fold, whilst grade 3 or above (high grade) hypertension risk was up to four times higher in treated patients.[26–28] Subgroup analyses from one large metanalysis revealed marked variability in hypertension depending on tumour type, VEGFR-TKI used, control therapy, and chemotherapy regimens: breast cancer patients had the greatest risk for any-grade hypertension, while the largest proportion of high grade hypertension was seen in prostate cancer patients treated with VEGF-TKIs.[27] Age, obesity and pre-existing hypertension are the key risk factors for development/worsening of anti-VEGF treatment-associated hypertension.[29,30]

The elevated hypertensive risk has also been demonstrated with newer multi-target (including VEGF) TKI's such as fruquintinib, anlotinib and apatinib: fruquintinib and alotinib were associated with 5–21% of grade 3 or above and 13–67% of any-grade hypertension.[31 32] In the REALITY RCT published this year, apatinib was associated with an even higher (34%) incidence of grade 3 or above hypertension.[33] Similarly Anlotinib, a novel TKI with multiple targets including VEGF, has also been strongly associated with hypertension with an incidence ranging between 13%−67% across clinical trials with severe hypertension reported between 4% and 16%.[32]

Clinical trials to date have highlighted the importance of early identification and treatment of hypertension along with tailored dosage regimens to reduce severe hypertension and discontinuation.

Comparative head-to-head data of treatment-related hypertensive rates between different VEGFi mAbs and VEGF-TKIs is limited. A subgroup analysis of a large systematic review of 77 phase III and IV randomised control trials between 1990 and 2014 showed no significant differences for incident hypertension and for most CVAE.[18] In contrast, a recent comparative network meta-analysis of over 20000 patients from 45 RCTs of nine VEGF-TKIs found that lenvatinib was the most likely to induce hypertension closely followed by vandetanib, cabozantinib, axitinib, pazopanib, sorafenib, sunitinib, regorafenib and nintedanib with no significant difference found for severe CVAE and severe hypertension.[34] Unsurprisingly hypertension is magnified with a combination of targeted anti-VEGF therapies as was demonstrated between axitinib and crizotinib.[35] A 2022 real-world Australian population study looking broadly at vascular signalling pathway inhibitor treatments, reported the incidence of new-onset and aggravated hypertension during treatment was similar, at 24% and 25% respectively, with a combined overall

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incidence of almost 50%, similar to clinical trial populations.[30] Similarly a 2022 review of both VEGFi oral TKI's and bevacizumab reported a median onset of 47 days for development of hypertension and importantly no difference in treatment interruption or discontinuation between treated groups due to hypertension.[36]

Building upon clinical effectiveness of VEGF inhibitors there has been an expansion of anti-angiogenic drugs in combination with other anti-neoplastic therapies such as with chemotherapy, and other targeted biological and immunotherapies. These combinations reduce treatment resistance and improve efficacy with promising results already realised in several cancers including melanoma, CRC, RCC, NSCLC, and glioblastoma.[37] These treatment combinations (e.g. Lenvatinib combined with EGFR targeted TKI gefitinib or pembrolizumab) have demonstrated improved anti-cancer efficacy compared with hypertension incidence comparable to monotherapy alone.[38–40] Similarly, trials of conventional chemotherapy combined with anti-angiogenic treatments (e.g. combination of etoposide with apatinib and docetaxel, epirubicin and cyclophosphamide with Apatinib in a recent 2022 publication) have also shown renewed treatment efficacy without significant unexpected hypertensive toxicity, with data predominantly showing higher rates of lower grade 1 and 2 hypertension.[41–44]

Interestingly, there is mounting evidence that VEGFi-induced hypertension, which is an "on-target" treatment response, may predict favourable cancer outcomes in patients and possibly represent a prognostic biomarker.[8,29,36,45–60] In SELECT trial of patients with advanced thyroid cancer, there was a significant association between Lenvatinib-induced hypertension and overall survival.[55] While similar findings have also been demonstrated with some other novel agents, eg anlotinib,[32] other studies have failed to corroborate this association, leading to knowledge gap.[51,61]

Predicting VEGFi induced hypertension has been an identified are of interest, there are currently no proven predictive serum biomarkers available in clinical practice to guide physicians when assessing their patients for these treatments.[62] Exploration has already begun into potential novel biomarkers such as VEGF-A and VCAM-1 which may utilised to predict hypertension in VEGFi treated patients. Most recently a study by Quintanilha et al found lower levels of these markers to be significant predictors of hypertension in colorectal patients treated with Regorafenib. Although not available in clinical use currently markers such as these may potentially path the way for tailored dosage regimens for patients and better help clinicians assess hypertensive risk and in doing so reduce treatment discontinuation or interruption.[63] There has been recent interest as to whether genetics may prove key to this issue and help both prediction of both treatment efficacy and hypertensive effects. Examples have been demonstrated in breast cancer patients treated with bevacizumab whereby certain genetic polymorphisms were associated with improved survival whilst others associated with lower severe hypertensive effects.[64] Similarly studies across a variety of tumours treated with bevacizumab have identified various single nucleotide polymorphisms (SNPs) of genes (WNK1, KLKB1, GRK4, SLC29A1 and HSP90AB1) which are involved in a wide array of mechanisms related to blood pressure regulation, these SNPs have been associated with the development of significant VEGFi related hypertension.[65,66] Further research into genetic polymorphisms associated

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with the development of hypertension in novel VEGFi treatments is slowly emerging, for example VEGFA and eNOS polymorphisms and sunitinib associated hypertension.[67] These associations will likely lead to a better understanding of the mechanistic influences underpinning the development of VEGFi hypertension and may one day lead to serum biomarkers to predict patient risk and treatment efficacy however larger clinical studies are required to validate findings such as these.

Recent research interest in the management of VEGFi induced hypertension and its effective management is evident by the diverse range of recent and ongoing clinical trials (CHA-RISMA (NCT04467021), NCT03709771, UNICO (NCT03882580) and TITAN (NCT01621659))[62] some of which aim to assess the clinical outcomes of VEGFRi treated patients whilst others have been specifically designed to assess the ideal BP targets for treated cancer patients to better guide clinical practice. Recent 2022 publication demonstrated in animal models (Wistar rats) treated with Axitinib that losartan, an established angiotensin receptor blocker, can be used to effectively reduce hypertensive effects without effect on antitumor activity.[68] A 2022 publication by Ren et al found that in metastatic CRC patients with bevacizumab related hypertension, treatment with renin-angiotensin inhibitors showed significant survival benefit over patients treated with calcium channel blockers or no treatment.[69] Interestingly Mice studies using lisinopril further demonstrated a positive synergistic anti-tumour effect with increased 5-fluorouracil (5-Fu) tissue penetration and decrease both collagen and hyaluronic acid (HA) deposition whilst significantly downregulating the expression of TGF-β1 and downstream SMAD signalling which may also improve anti-tumour effect.[69] These findings may suggest ACE-I as a class may be a favoured first line anti-hypertensive therapy in selective cancer patient populations. Efforts have been made to explore novel treatments for VEGFi hypertension utilising preclinical animal models and pluripotent stem cell models[70], for example the use of rodent models to explore Endothelin blockade therapies[71] and targeted treatments (Sildenafil) to utilise the NO regulatory pathway.[72]

Mechanisms of VEGFi induced hypertension

Our current knowledge of VEGFi-induced hypertension largely stems from an established understanding of chemotherapy-induced hypertension which revolves around two major mechanisms: endothelial dysfunction and microvascular rarefaction.[8,13,19,45,73–76] VEGF signalling pathway disruption/inhibition is a critical factor leading to endothelial dysfunction in numerous chemotherapies. Despite their established use, a complete understanding of the molecular processes driving VEGFi-induced hypertension and vascular toxicities remains unclear. The key underlying mechanisms likely include inhibition of endothelial nitric oxide synthase (eNOS), diminished nitric oxide (NO) production, oxidative stress, activation of the endothelin-1 system promoting vasoconstriction, and rarefaction (Figures 1 and 2).[19,32,75,76]

Microvascular rarefaction may occur when antiangiogenic therapy reduces the microvascular surface area whilst increasing vascular resistance and blood pressure.[77] It was thought that chronic VEGF depletion leads to reduced microvascular endothelial cell survival and consequently reduced tissue microvascular density.[77] Formation of local thrombosis leads to a further decrease in vascular perfusion and exacerbates endothelial cell apoptosis

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and microvascular obliteration. These cumulative effects lead to increased systemic vascular resistance, resulting in a further increase in blood pressure. However, the role of microvascular rarefaction in antiangiogenic therapy-induced hypertension remains conflicting.[78] Preclinical studies in mice treated with small molecule VEGF inhibitors showed that up to 30% of capillary networks regress by 21 days of therapy and reverse with therapy discontinuation. In humans, the capillary density in patients receiving Bevacizumab was only reduced by ~10% after 6 months of treatment and was associated with the increased blood pressure,[79] while another study reported ~20% reduction in capillary density after 5 weeks of therapy with VEGF-TKI Telatinib.[80] However, the time course for capillary rarefaction of several days to weeks does not match the rapid rise in blood pressure observed in patients who started antiangiogenic therapy. It is likely that capillary rarefaction does play a role in antiangiogenic therapy-induced hypertension but is not the sole factor in its development.

Animal studies have provided key insights into the mechanisms of antineoplastic treatment related hypertension.[81] A landmark study by Facemire et al demonstrated that mice receiving anti-VEGFR-2 antibody rapidly developed hypertension.[82] The NO synthesis inhibitor L-NAME administration abolished the difference in blood pressure between the vehicle- and anti-VEGFR2-treated groups. Thus, this suggested that VEGFi-induced hypertension is mediated by NO inhibition.[82] Another study in C57BL/6 mice showed that administration of a single-dose aflibercept led to a rapid and dose-dependent elevation in systolic blood pressure associated with NOX1/NOX4-mediated ROS accumulation, impaired AKT/eNOS/NO signalling and EDR, reduced intracellular levels of L-arg, and decreased expression of CAT-1.[83] L-arg supplement significantly inhibited aflibercept-induced hypertension once again highlighting the role of NO signalling VEGFi-induced hypertension and potential therapeutic utility of L-arg in this setting.[83]

Additional postulated mechanisms for TKI-induced hypertension relate to interruption of downstream intracellular VEGF signalling and include decreased renal NO bioavailability via downregulation of soluble guanylate cyclase activity, inhibition of intrarenal NOS activity, activation of the renin-angiotensin-aldosterone system, and decreased fractional sodium excretion.[84] Other mechanisms suggested for VEGFi-induced hypertension include impaired sodium balance resulting in salt-sensitive hypertension[23] due to impaired buffering of salt in the skin and the development of vascular stiffness which may occur within the first few weeks of treatment with sunitinib[85] and sorafenib[86]. Soluble Fms-like tyrosine kinase 1 (sFlt-1) was recently shown to inhibit angiogenesis and lead to cardiac toxicity.[87] Similarities between the pathophysiology of VEGFi-induced hypertension and the role of VEGF, sFlt-1 and endothelin-1 in the development of preeclampsia[88,89] have also been drawn and this remains an area of interest which may provide further insight and understanding of VEGFi-induced hypertension and vascular toxicity.[90]

Interestingly, a recent study showed that Apatinib treatment increased blood pressure in Wistar–Kyoto rats by causing a marked increase in intralaminar distances and collagen deposition in mid-aorta tissues.[91] These Apatinib-induced vascular remodelling were reversed following the treatment with Y27632, a nonspecific RhoA/Rho kinase (ROCK)

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inhibitor.[91] Therefore, the ROCK signalling pathway could be an important mechanism of hypertension while ROCK inhibitors have emerged to be attractive anti-hypertensive drugs.

BRAF-MEK Inhibitors

Targeted B1 homolog v-raf murine sarcoma viral kinase oncogene (BRAF) and *mitogen-activated protein kinase (MEK)* inhibition disrupts the crucial RAS-RAF-MEK-ERK signalling pathway which drives cell differentiation, proliferation and provides resistance to apoptosis. In certain types of malignancy activating somatic point mutations in BRAF or downstream along the signalling pathway lead to upregulated and unbalanced cell propagation and survival.[92]

BRAF inhibitor use has shown significant improvements in progression-free and overall survival across a range of malignancies with greatest effect in metastatic melanoma, hepatocellular carcinoma, thyroid cancer, renal cell carcinoma, gastrointestinal stromal tumours, colon cancer and non-small cell lung cancer.[8,93] BRAF resistance through reactivation of the MAPK pathway[94] has emerged as a limiting step in the use of these agents in clinical practice, leading to the development of combination BRAF inhibitors with other therapies targeting downstream signalling pathways.[93,95] MEK inhibition is one of the major downstream targeted strategies to overcome BRAF resistance, with several approved combination BRAF/MEK inhibitors (vemurafenib [BRAF]/cobimetinib [MEK], dabrafenib [BRAF]/trametinib [MEK], and encorafenib [BRAF]/binimetinib [MEK]) which have shown improved antineoplastic efficacy particularly in the metastatic setting.[95–97]

BRAF and BRAF-MEK inhibition is associated with a range of significant cardiac adverse events including cardiac failure with reduced ejection fraction, atrial fibrillation, QT prolongation, cardiac hypertrophy and arterial hypertension.[97,98] Both BRAF-specific therapies (vemurafenib and dabrafenib) as well as multi-targeted BRAF-inhibiting TKIs (sorafenib and regorafenib) can induce hypertension which predisposes patients to further cardiovascular toxicity.[98]

Clinical and epidemiological evidence for BRAF-MEK inhibitor-induced hypertension

A review of BRAF inhibitor (Sorafenib, vemurafenib, Regorafenib and Dabrafenib) clinical trials highlighted the potential cardiovascular toxicity of BRAF inhibition as a class, with Regorafenib having the highest mean occurrence of all-grade hypertension (37.5%).[99] MEK inhibitors are also associated with significantly increased occurrence of hypertension: in METRIC trial of trametinib compared with standard chemotherapy in metastatic melanoma, the incidence of all-grade and grade 3 hypertension was 15% and 12%, respectively in trametinib treatment arm compared to 7% and 3%, respectively in the chemotherapy treatment arm.[100] A meta-analysis reported a relative risk increase of 1.5 for hypertension and 1.85 for high-grade hypertension in patients treated with MEK inhibitors compared to control patients, with no significant difference in hypertensive risk between individual agents.[101]

Over the last decade, there have been multiple trials (COMBI, coBRIM and COLUMBUS) and meta-analyses which have consistently demonstrated a significantly higher risk of

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hypertension with combination BRAF-MEK inhibitors relative to single agent BRAF therapies (Table 3).[96,98,102] In the largest review to date across two national registries, the overall combination therapy incident hypertension was significantly higher (ROR 1.75) compared with BRAF inhibitor monotherapy with a difference appreciated within the first 6 months of treatment.[98] Further assessment of combination treatments with Encorafenib and Binimetinib are underway with preliminary results expected to be published late in 2022. Of note, an important exclusion criteria of most BRAF-MEK inhibitor trials was patients with pre-existing clinically significant cardiac disease or cardiac dysfunction,[103] which could potentially underestimate the real world incidence of CVAE.

The expanding development and application of BRAF-MEK inhibitors has led to trials of "triplet" treatment combinations such as with immune checkpoint inhibitors[104,105], PARP inhibitors and EGFR inhibitors[106] which may improve resistance to BRAF-MEK available treatments and efficacy for patients. While limited, there are data from trials in advanced BRAF-mutated melanoma, which compared addition of pembrolizumab or placebo to a combination of dabrafenib and trametinib, of higher incidence of grade 3 hypertension (8.3%) in the "triplet" therapy group compared with the placebo group (3.3%).[107] This highlights the potential for even greater incidence of hypertension and other CVAE with multi-combinations therapies.

Mechanisms of BRAF-MEKi-induced hypertension

The RAS-RAF-MEK-ERK pathway is important in cell repair, proliferation and survival and has been shown to be involved in pathogenesis of hypertension and other CVD.[108–111] Although the exact mechanism of BRAF-MEK inhibitor-induced hypertension remains unclear; indirect inhibition of MAPK pathway has been postulated to be involved in the pathological development of cardiac hypertrophy and dysfunction.[93,97] It has been proposed that BRAF/MEK inhibitors lead to CD47 upregulation in cells via rebound ERK activation,[112] which results in the inhibition of both NO bioavailability and soluble guanylate cyclase activation propagating endothelial dysfunction, vasoconstriction and the development of hypertension.[102,113] Yet, inhibition of ERK1/2 activation in development of cardiotoxicity have yielded discordant results: trametinib is thought to lead to cardiotoxicity via inhibition of ERK1/2 activation,[114] while dabrafenib, was shown to be cardioprotective *in vitro*, via inhibition of Raf kinase pathway, disrupting ERK1/2 signaling.[115]

Bruton tyrosine kinase inhibitors (BTKi)

Bruton tyrosine kinase (BTK) inhibitors (BTKi) act by selectively targeting and irreversibly disrupting the BTK downstream of the B cell receptor preventing chemokine-induced adhesion and migration.[84,116] Overall BTKi have shown dramatically better efficacy across a range of hematological malignancies than traditional chemoimmunotherapies (CITs) and are well tolerated, however accumulating data have revealed multiple adverse events, including CVAE.[117]

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Clinical and epidemiological evidence for BTKi-induced hypertension

A pooled analysis of 424 patients from three phase III trials on ibrutinib therapy for CLL reported incident hypertension in 18% of patients with severe grade hypertension occurring in 6%, with similar results reported in an extended phase 3 RESONATE-2 clinical trial.[118,119] A recent meta-analysis of 8 randomised control trials reported a risk ratio of 2.85 for development of hypertension on ibrutinib.[120] In a detailed review of 562 patients treated with ibrutinib over a 7 year period, 78% patients developed new or worsening hypertension, with incident hypertension in 71% and high grade hypertension (>160/100 mm Hg) 17% of those with pre-existing hypertension.[121] The true incidence of hypertension was suggested to be even higher during real world experience.[122] Reassuringly treatment for hypertension reduced the risk of MACE (hazard ratio 0.4) regardless of antihypertensive drug selection.[121]

In addition, ibrutinib has been associated with other cardiovascular toxicities including atrial fibrillation and bleeding, however next generation, more selective BTKi (acalabrutinib and zanubrutinib) seem to have an overall lower cardiovascular toxicity, including hypertension.[117] Like ibrutinib, acalabrutinib (second generation BTKi), was also trialled in refractory CLL patients and similarly demonstrated a treatment related hypertensive incidence of 7%.[123] However, more recent experience with acalabrutinib from the ELEVATE-TN trial[124] and also the ASCEND trial[125] suggests lower rates of hypertension, with comparable rates of all grade and severe grade hypertension as control treatment groups.[124,125] Similarly, evidence from the ASPEN trial showed a comparatively lower incidence of hypertension and a significantly lower hazard ratio of 0.59 amongst patients treated with the novel agent zanubrutinib compared with ibrutinib.[126] While these data are encouraging, the most recent assessment from a 2022 publication of 280 patients treated with Acalabrutinib found that almost half developed or experienced worsening hypertension over 41 months with 53% developing new hypertension at one year with 1.7% having severe hypertension (≥grade 3).[127] Moreover there was a significant correlation between the degree of SBP rise following initiation and predicted MACE risk suggestive of an adverse class effect from BTKi and opposing recent opinion that newer generation BTKi may cause less hypertension.[127] Importantly the study demonstrated there was no single anti-hypertensive treatment which was found to prevent this hypertensive effect.[127] These opposing data presented support the need for further larger clinical trials and real world studies to properly ascertain the true hypertensive effects of the newer generation BTKi treatments.

Mechanism of BTKi-induced hypertension—Evidence of the underlying mechanism by which BTKi are associated with the development and worsening of hypertension is limited. However, it has been suggested that a decrease in downstream heat shock protein 70 (hsp70) may be associated along with decreased phosphatidylinositol 3-kinase (PI3K) signalling resulting in downstream depletion of NO production and reduced VEGF propagation with eventual vascular remodelling, and endothelial cell dysfunction.[13,121,128,129]

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Phosphatidylinositol 3-kinase inhibitors (PI3Ki)

PI3K inhibitors (PI3Ki), including the pan-PI3Ki copanlisib and isoform specific PI3Ki alpelisib, idelalisib, umbralisib and duvelisib, work via inhibition of the PI3K enzyme signalling pathway which is essential for a diverse range of cell functions including cell survival, metabolism, immune function and cell division.[130,131] Upregulation through mutation within one of the four isoforms of the class 1 PI3K enzymes often found within immune cells and has been implicated in malignancies such as lymphoma, glioblastoma, ovarian, endometrial, breast, colorectal, gastric and prostate cancers.[131,132] A major challenge for this class of treatments has been to overcome significant non-CV toxicities including hyperglycaemia, multiple gastrointestinal side and myelosuppression.[131,133] Hypertension has been less commonly recognised as a significant adverse reaction of PI3Ki, however does need to be considered by treating clinicians.

Clinical and epidemiological evidence for PI3Ki-induced hypertension

CHRONOS-1 study of indolent B cell lymphoma with intravenous copanlisib reported any-grade hypertension incidence of 29.6% and grade 3 or above hypertension incidence of 23.2%.[132] Hypertensive effects of copanlisib appear to be rapid in onset, within 2 hrs of starting treatment, and do not appear to be lasting, however the mechanism of this transient effect is unknown.[134] Copanlisib combinations with MEK inhibitor Refamentinib[135] or HER2 inhibitor trastuzumab[136] have been associated with an even higher incidence of grade 3+ hypertension of 26% and 33%, respectively.

Hypertension does not appear to be class effect of all .PI3Ki[131,137] Isoform specificity of certain PI3K inhibitors such as idelaslisib, umbralisib, duvelisib, parsaclisib[138] and dactolisib[139] have resulted in a different adverse effect profile with lower overall rates of hypertension,[131] compared to pan-PI3Ki copanlisib.[140,141] This difference may also be in part attributed to drug delivery method (intermittent intravenous infusion opposed to regular oral dosing).[13,133]

Mechanism of PI3Ki-induced hypertension—Although the pathophysiology behind PI3Ki-induced hypertension is not yet characterised it is postulated that PI3K plays a role in the endothelial cell function, whereby inhibition results in endothelial dysfunction and vasoconstriction.[142] Furthermore, PI3K isoforms may help regulate blood pressure via type-1 angiotensin-receptor signalling which has led to exploration of the therapeutic anti-hypertensive utility of this pathway.[134] PI3K pathway may also play a significant role in pathologic remodelling, hypertrophy and contractility in the heart which should encourage a degree of caution for cardiovascular toxicities particularly amongst the elderly whilst taking these medications.[143] Interestingly, disruption of this cascade pathway via PI3K isoform inhibition has been investigated both in-vivo and various animal models with promising results in the prevention and progression of pulmonary hypertension.[144] This has led to recent increasing interest in the inhibition of the PI3K-AKT pathways as a novel therapeutic target for the treatment of evolving and established pulmonary hypertension, which carries significant morbidity and mortality for patients.[145]

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RET kinase inhibitors (RETi)

RET is a transmembrane receptor tyrosine kinase, critical for the development of multiple tissues.[146] RET activation, either wild-type or through mutations, promotes tumour growth and contributes to development of NSCLC, papillary thyroid cancers, and other cancers.[146,147] This led to the development of both multikinase inhibitors with RET inhibitor (RETi) activity (Vandetanib and Cabozantinib) and selective RETi (Pralsetinib and Selpercatinib) that are highly potent with a better toxicity profile.[147]

Clinical and epidemiological evidence for RETi-induced hypertension

Hypertension has been associated with RETi, which has only recently been demonstrated in several trials of Selpercatinib and Pralsetinib, as well as retrospective real world safety analysis of Selpercatinib, with any-grade hypertension rate of 31–43%, and severe grade hypertension rate of 14–21%.[148–151]

Mechanism of RETi-induced hypertension—Similar to most other kinase inhibitors, the specific mechanism by which RETi cause hypertension remains unclear. However, given that RET kinase plays a role in the RAS-RAF-MEK-ERK signalling cascade, it has been proposed that the mechanism is similar to that seen with BRAF-MEKi, i.e. rebound ERK activation and CD47 upregulation leading downstream hypertensive effects,[152] as discussed in the BRAF-MEKi section above. This is supported by the *in-vitro* studies which identified upregulated K-RAS protein in RETi-treated patients, which may be a sign of rebound ERK activation and potential treatment resistance;[153] however, this remains speculative. Furthermore, the selective RETi Pralsetinib and Selpercatinib have greater intracranial efficacy and improved penetration into the central nervous system compared to the previous multikinase TKIs.[154,155] Thus, long-term monitoring will be crucial to identify any potential adverse effects on the development and function of neurons following suppression of RET activity.[156]

Proteasome inhibitors

Proteasome inhibitors (PI) have a defined role both as single and combination therapy in the treatment of lymphoma and multiple myeloma with their efficacy related to the regulation of protein degradation.[157] Proteasomes are important for normal cell function, and also particularly for susceptible malignant cells, as they help maintain protein homeostasis via clearance of cytotoxic or misfolded proteins, which would otherwise threaten cell survival and propagation.[157] Currently there are three PI in clinical use – first generation reversible PI Bortezomib, and two second generation irreversible PI – Carfilzomib and Ixazomib.

Clinical and epidemiological evidence for PI-induced hypertension

Bortezomib and carfilzomib are both effectively used in the treatment of multiple myeloma. Both have been implicated in chemotherapy-induced hypertension, with carfilzomib having a more significant pro-hypertensive effect than bortezomib.[158] In Phase III ENDEAVOR trial, hypertension (16% of patients on carfilzomib and 6% on bortezomib) was reported as one of the most frequent grade-3+ CVAE.[159] Hypertension was also reported in 14.3% of

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PI-treated patients in one of 4 phase II studies.[160] Recently, data from the SEER-Medicare dataset inclusive of 815 carfilzomib treated patients, found a hazard ratio of 1.41 for all CVAE, with hypertension reported in 27.6% patients with a hazard ratio of 3.33 compared to non-carfilzomib patients.[161] A meta-analysis suggested that hypertension, the commonest reported CVAE, may be more frequent with carfilzomib as opposed to other PI's, and also with combination therapy, especially with immunomodulatory agents, than PI monotherapy.[162] Orally-bioavailable Ixazomib is reported to have an improved toxicity profile, especially peripheral neuropathy, however, cardiovascular toxicity remains a recognised ongoing issue,[163] with incidence rates of severe grade 3–4 hypertension between 5–20%.[164,165]

Mechanisms of PI-induced hypertension

The underlying mechanism of PI-induced hypertension remains unknown. Given the PI mechanism of action, it was postulated that it could be associated with abnormal accumulation of ubiquitinated or misfolded proteins from proteasome inhibition.[166] Carfilzomib decreases proteasomal activity *in-vitro* and *in-vivo* with subsequent increased PP2A activity, decreased AMPKα phosphorylation, and upregulated eNOS, Bip, Raptor, and enhanced LC3B-dependent autophagy.[166] Chronic proteasome inhibition with another PI (MLN-273) has been associated with increased oxidatively (4-hydroxy-2-nonenal [4-HNE])-modified proteins, NOX subunit p47phox, and eNOS levels in coronary arteries.[167] Furthermore, MLN-273 also impaired coronary endothelium-dependent vasorelaxation and intimal thickening, resembling and aggravating the vascular effects of traditional cardiovascular risk factors such as hypercholesterolemia.[167]

Interestingly, Bortezomib treatment was reported to attenuate hypoxia-induced elevation of Ca^{2+} and alleviate pulmonary hypertension in hypoxia- and monocrotaline-induced rat pulmonary hypertension models.[168] In contrast, Carfilzomib treatment impairs Ca^{2+} transients and contractility of cardiomyocytes in conjunction with decreased expression of genes associated with Ca^{2+} handling (e.g., SLC8A1 [solute carrier family 8 member A1], RYR2 [ryanodine receptor 2], CASQ2 [calsequestrin 2], and ATP2A2 [ATPase sarcoplasmic/endoplasmic reticulum Ca^{2+} transporting 2]).[169] These recent results indicate a potential role of Ca^{2+} handling in PI-induced hypertension and may, in part, explain the differential toxicity profile of PIs.

Poly (ADP Ribose) Polymerase inhibitors (PARPi)

Poly(ADP-ribose) polymerases (PARPs) play a crucial role in the normal DNA repair of single-strand breaks, along with several other diverse functions. PARP inhibition (PARPi) is a novel and effective therapeutic strategy for targeting malignancy,[170] especially for breast, fallopian, peritoneal and ovarian cancers expressing BRCA1 and BRCA2 germline mutations[170] and for pancreatic and metastatic castrate resistant prostate cancers with mutations leading to impaired homologous recombinant repair.[171] PARPi are used both as monotherapy and in combination with other agents, including immune checkpoint inhibitors, VEGFi, TKI and traditional chemotherapy to improve patient outcomes.[171,172]

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Clinical and epidemiological evidence for PARPi-induced hypertension

As PARPi have been introduced into the oncological armamentarium, clinical studies suggest a differential effect of Niraparib versus other PARPi on blood pressure.[173] Concerns for hypertension stem from the ENGOT-IVA16/NOVA clinical trial, which assessed Niraparib maintenance therapy in recurrent ovarian cancer, and reported any-grade hypertension and grade 3/4 hypertension in 19% and 8% of patients the treatment arm, respectively compared with 4% and 2% of patients in the placebo arm, respectively.[174] The recently published (NCT03404960) trial with ongoing follow up assessing niraparib plus either nivolumab or ipilimumab in patients with advanced pancreatic cancer showed ≥ grade 3 hypertension in approximately 8% and 9% respectively in both treatment groups containing niraparib, a result in keeping with previous clinical trial data.[175] Other reported associations between PARPi and incident hypertension have come from smaller clinical trials combining VEGFi, chemotherapies with PARPi therapies,[176,177] likely confounded by the known association between VEGFi and hypertension.

However, other PARPi including olaparib, rucaparib, and talazoparib are generally not implicated in development of hypertension. It may be the case that some PARPi may even reduce the risk of hypertension. This was supported by the results from the PAOLA-1 trial, which showed that fewer participants in the olaparib combination with bevacizumab group experienced hypertension compared to the placebo and bevacizumab combination group.[178] This concept that PARPi may play a cardioprotective role had also been identified in earlier preclinical animal models.[179] The underlying protective mechanism of PARPi may be explained by the suggested role PARP-1 activation has in the development of atherosclerotic lesions, myocardial dysfunction and hypertension[180], possibly driven by angiotensin-II signalling. Ongoing investigations into the use of PARPi in prevention of fibrosis[181] may yield a better understanding of PARP-associated hypertension, and the potential protective cardiovascular effects of PARPi.

Mechanisms of PARPi-induced hypertension

To date, the mechanism(s) underlying the pro-hypertensive effect of Niraparib remain unknown. Given that Niraparib can interacts with various neurotransmitter transporters, it has been speculated that an off-target effects on vasoactive receptor binding of transports for dopamine, norepinephrine and serotonin, may result in overall reduced cellular uptake of dopamine and norepinephrine, which may contribute to hypertension.[173] Hypertension associated with Niraparib may be explained via the inhibition of DYRK1A which could in turn see increased levels of the previously mentioned neurotransmitters in turn promoting inotropic increase and hypertension.[182,183] Niraparib has the distinct pharmacological action to inhibit dual-specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A) and potentially contribute to hypertension.[182,184] DYRK1A has been shown to play an important role in regulating the turnover of monoamine neurotransmitters (i.e., dopamine, serotonin and noradrenaline), whereby studies showed a strong relationship between DYRK1A expression and the dopaminergic system.[182] DYRK1A overexpression induced dramatic deficits in the levels of dopamine, serotonin and noradrenaline in certain regions of the brain.[182] Therefore, the inhibition of DYRK1A by Niraparib may have inotropic effects on the heart and potentially causes high blood pressure (hypertension). Interestingly,

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previous studies also showed that DYRK1A also plays a role in circadian rhythm.[185,186] By cooperating with glycogen synthase kinase 3β (GSK-3β), DYRK1A regulates the rhythmic Ser557 phosphorylation-triggered degradation of cryptochrome-2 (CRY2).[186] Knockdown of DYRK1A consequently led to abnormal accumulation of cytosolic CRY2, advancing the timing of a nuclear increase of CRY2, and shortened the period length of the cellular circadian rhythm.[186] Emerging evidence are suggesting that the molecular circadian clock plays a crucial role in blood pressure control[187–189], thus disruption of the circadian rhythm may potentially cause hypertension. These findings could be important for the selection of PARPi for cancer patients.

With the increasing use of more novel anti-angiogenic therapies alone or in combinations with, there must be a balanced appreciation of severe adverse side effects and cardiovascular risk which has been previously cautioned within the literature and needs to be diligently assessed and managed.[190]

Figure 2 summarizes the known mechanistic signalling cascades implicated in development of hypertension across all the anti-cancer medication classes described above.

The long-term outcomes of cancer therapy-related hypertension—There is evolving interest in gaining insight into the true ramifications which cardiovascular diseases such as hypertension and in particular cancer treatment-related hypertension may have on both long term patient morbidity and mortality.[191] The data for long term outcomes of therapy-related hypertension is extremely limited and in general long term CVD for cancer patients has often been extrapolated from childhood cancer survivor cohorts however these data may not be accurate given the exponential growth in available novel anti-cancer therapies over the last decade. Nevertheless, poorly controlled hypertension is a clear risk factor of development of heart failure during treatment with anthracyclines, ibrutinib and VEGFi.[117,192–194] The National Cancer Institute has previously identified CVD as a key clinical manifestation of aging in cancer survivors[195] and a factor that crucially can be identified early and either prevented or efficiently managed making a strong and valid point that more needs to be done in the way of screening and managing the long term CVD risk of these cancer survivors.[196]

Similar to historic data, recent evidence from the analysis of large cohort reviews of several different populations has shown that cancer and cancer-therapy amongst cancer survivors is associated with significant increase in cardiovascular disease risk.[197,198] An observational analysis of a US population inclusive of over 1.2 million cancer patients with 28 different cancer types identified approximately 11% of cancer patients died from CVDs, 76% of these were due to heart disease. The mortality risk was greatest in cancer patients diagnosed at a younger age (<35), with the highest CVD mortality in the first 12 months from diagnosis.[199] The most recent data from a 2022 publication of retrospective cohort Canadian population data inclusive of over 4.5 million patients with a new cancer diagnosis compared with a non-cancer cohort over an 11 year period demonstrated hazard ratio of 1.33 (95% CI: 1.29–1.37) for CVD mortality. The data conveyed that comparatively, cancer patients had approximately a 60% increase in the relative risk of cardiac failure, 44% increased risk of stroke and over three times the risk of pulmonary embolus. Concerningly the prevalence of

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almost all cardiovascular risk factors was significantly elevated within the cancer population cohort (diabetes 10% vs 3%, severe obesity 17% vs 11%, dyslipidaemia 24% vs 22% and atrial fibrillation 3% vs 1%) with a striking difference in hypertension rates between the cancer and non-cancer cohorts of 31.7% vs 10.7%.[200] The results convincingly demonstrate that a new cancer diagnosis correlated with both CVD morbidity and mortality risk even after adjustment for baseline CV risk. Furthermore this CVD risk for several measured outcomes was consistently demonstrated out to 10 years similar to previous evidence from both large observational population studies[199] and smaller targeted studies such as CAROLE (Cardiac-Related Oncologic Late Effects)[201] further strengthening the concept of persistent cancer and cancer therapy-related CVD risk. In keeping with these findings previously reported evidence from the breast cancer SEER dataset has suggested that cancer may be an risk factor for CVD independent of cancer treatments such as chemotherapy or radiation therapy.[202]

Much of the long term CVD outcome data has arisen from well-established chemotherapeutic agents such as anthracycline and platinum based chemotherapy and from patients treated with radiation therapy.[203–205] In an era of rapid evolution of targeted cancer therapies there is an obvious void in available long term population data about the specific long term CVD risks associated and the absolute impact novel therapies will have on both CV morbidity and mortality. It is important to recognise that although effective management and early intervention for CVD related to cancer treatment has been instituted into clinical practice in many oncology and cardio-oncology centres around the world the implementation of CV screening and management of disease risk is often not continued as routine practice in long-term survivors.[191]

An optimistic outlook can be had that we will see a more complete understanding of the long-term cardiovascular consequences of pro-hypertensive cancer therapies given the pace of progress within the field of cardio-oncology itself. However, this will require several important changes such as:

- Increasing the scope of CVD screening and the duration of follow up of cardio-oncology patients beyond there discharge from active treatment.
- Improving the communication and data sharing between all practitioners involved in cancer patients care and encouraging the education and awareness of silent and often overlooked cardiovascular sequalae of treatment such as treatment related hypertension which may not be apparent until several months or even years following treatment.
- Improved uptake and active participation of multiple collaborations and cardio-oncology centres in data sharing of patient outcomes related to treatments.
- Capturing important data points which are currently lacking including therapy-related CVD complication data with a focus on both old and the new and emerging cancer therapies in clinical practice.

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- Most importantly re-innovation and institution of improved clinical trial design with the aim of more extended follow-up periods and improved patient retention allowing for the capture of these important long term data points.

Hypertension as a risk factor for cardiotoxicity—Hypertension is the most prevalent modifiable risk factor for the development of cardiovascular disease[206] and is an issue that persists following acute cancer treatment, plaguing both adult[207] and childhood cancer survivors later in their lives. Rates of hypertension in cancer survivors are as high as two and a half times that of the adjusted general population,[208] further adding to an already increased CVD risk and CVD mortality in cancer survivors.[209–211] Recently published observational cohort data demonstrated childhood cancer survivors had higher rates underdiagnosed CVD risk factors, most concerningly these patients were significantly undertreated compared with the standard matched American population (21.0% versus 13.9%, P=0.007) with hypertension being the most prevalent undertreated risk factor at 18.9%. This may in part be due to lower rates of health-related self-efficacy which crucially highlights a need for focused care from cardiologists and general care practitioners to address cardiovascular risk modification and improve cancer patient self-efficacy by effectively engaging them with responsibility in their own care decisions and management.[212]

CVD mortality in cancer patients can be described as a “multiple-hit” paradigm, with hypertension and CVD compounding the mortality risk in a complex interplay of overlapping risk factors including direct treatment toxicity, premorbid CV disease and lifestyle and behavioural risk factors.[213] Similarly in most recently published literature a “multiple strike theory” conveys the complex interplay of genetic predisposition for common cardiovascular disease and cancer risk factors (genes such as TTN, Tet2, PHTF1 and DDR) and exogenous factors (smoking, radiation, age, metabolic syndrome and environmental factors). These elements which taken in combination with anti-cancer therapies and treatments for CVD perpetuate poor short and long term outcomes for cancer patients.[214]

Furthermore several factors often overlooked when assessing both hypertension and CVD risk within cancer patient populations such as advances in cancer and cardiovascular disease screening, increased public awareness and engagement with their own health, improved therapies and imaging techniques, prolonged survival post treatment and of most significance an escalating aging population could indicate we may be on the verge of an even larger expansion era for cardio-oncology and its treatment related issues.[215,216]

An overt deficiency of standardised CV risk assessment tools established and validated for use in cancer patients and survivors, highlights a significant deficit in care within this population. An explanation for this may be that most cardio-oncology and cancer patient trials include younger, typically low-risk populations and the application of CVD risk assessment/predictive tools may falsely underestimate cardiovascular risk and events which may not be reflective of real world practice and therefore incorrectly guide treatment decisions. Furthermore limited sample sizes, CV event rates, lack of accurately captured CV data, vast heterogeneity amongst cancer therapy trial populations and short trial follow up

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durations make risk assessment tools and cardioprotective strategies difficult to accurately assess and validate.[217]

Efforts have been made by the European Society of Cardiology (ESC) in collaboration with the International Cardio Oncology Society (ICOS) to develop risk assessment tools to guide screening and decision making for cancer patients in clinical practice,[218] but these have not yet achieved widespread use.

Defining cancer therapy-related hypertension

Despite the established use of many anti-cancer therapy classes covered in this review, optimal blood pressure (BP) targets and therapeutic strategies for hypertension are largely based on broader general hypertension recommendations, which have not been widely validated in cancer populations.[219–224] Furthermore, hypertension guidelines are commonly generalised both to a variety of cancers and their respective treatments, which fails to account for the complexity and heterogeneity of different cancers, the vast array of anti-neoplastic treatment mechanisms and the individual patients. This poses the question: “does one size fits all approach is still appropriate within growing cancer populations?”.

Treatment-related hypertension can be of various grades and can be defined as systolic and/or diastolic BP increase following initiation of cancer therapies without other contributing changes.[225] There have been considerable efforts from various collaborations (CTCAE version 5[226], ACC/AHA 2017[224], ESC 2018[220], ISH-2020[223]) to define parameters around hypertensive toxicity and treatment related hypertension amongst cancer patients[97,121,227–229]. In an effort to formalise and simplify such recommendations a recently published IC-OS 2021 consensus statement has been released which defines normal SBP ≤130 mmHg and DBP ≤80 mmHg within the cancer population cohort.[225] Treatment initiation is recommended with antihypertensive therapy for patients prior, during or post cancer therapy above theses office/practice BP cut-offs if CVD risk ≥ 10% otherwise treatment should be initiated when BP exceeds SBP ≥140mmHg or DBP ≥ 90mmHg.[225] A rise in SBP>20mmHG or mean arterial BP >15mmHg are considered exaggerated responses and also prompt the consideration of therapy.[225] Importantly cancer therapy should be withheld with SBP≥180mmHg and DBP≥110mmHg and patients with a hypertensive emergency response causing end organ damage need immediate intervention in the particularly vulnerable cancer patient population.[225] Recently published first international cardio-oncology guidelines, developed jointly by the ESC, ICOS, European Hematology Association (EHA) and the European Society for Therapeutic Radiology and Oncology (ESTRO), provide a “sliding scale” thresholds for treatment of cancer therapy-associated hypertension based on the cancer metastatic state and prognosis (Figure S1).[230]

Screening and management of cancer-therapy associated hypertension

All physicians involved in the care of cancer patients face challenges in balancing adequate oncological treatment with acute and chronic cardiotoxicity associated with cancer therapies. Cardiotoxicities, including hypertension, may influence decisions around the type and duration of cancer therapy, which may ultimately impact on the overall survival outcomes

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for patients.[73] The goal of management of these patients is to provide individualised care by prevention, mitigation and appropriate management to minimise cardiovascular risk without disruption to cancer treatment throughout patient's cancer journey.[225,231]

Screening for Hypertension and therapy-related Hypertension in the cancer patient population

Hypertension screening and monitoring in cancer patients requires a detailed CVD and CV risk factor history, diligent cardiovascular exam for end-organ involvement, and most importantly, accurate BP assessment and monitoring, ideally with out of office methods (ambulatory or home BP monitoring)[227], given the considerable inaccuracy within the office setting[232].[19,228,233]. However, it is important to acknowledge the limited evidence for ambulatory BP monitoring within cancer populations, and a need for further research to establish the optimal approach. Different proposed pharmacologic management pathways for hypertension in cancer patients have been documented in recent literature and are not the focus of this discussion. However, a well summarised and up-to-date pathway for management has just been published as part of the first international cardio-oncology guidelines, developed jointly by the ESC, ICOS, EHA and ESTRO (Figure S2).[230]

Further investigation to compliment Hypertensive and CVD screening within the cardio-oncology setting may also encompass a multi-marker approach to assess for cardiac dysfunction and improve initiation of cardio-protective measures.[217,219,234] This may include the use of transthoracic echocardiography with Global Longitudinal Strain (GLS), 3-D Left Ventricular Ejection Fraction (LVEF) assessment and cardiac MRI imaging.[217,235,236] The use of Troponin, Naturetic Peptide and D-Dimer biomarkers have an established role in cardio-oncological workup for cardio-protective screening[237] particularly in the setting of cancer therapies known to cause cardiac dysfunction however there use as a marker for hypertensive heart disease has not been described in the literature.

Lifestyle interventions

Addressing the care needs and gaps for cancer patients/survivors will require improved efforts to appropriately manage modifiable CVD risk factors,[238] including lifestyle factors contributing to hypertensive risk.[239] Our increasing understanding of hypertension in cancer patients has unveiled the complexity of the multiple environmental and patient factors contributing to its development, including the role of polygenic risk,[240] while the roles of physical factors such as diet, obesity, sedentary lifestyle, smoking, excessive alcohol intake, diabetes and metabolic syndrome, kidney diseases, sleep apnoea, recreational drug use and non-physical attributes such as psychological stress and cancer-related pain are less well studied in cancer patient populations.[213]

In general population, major lifestyle interventions such as regular exercise, minimisation of alcohol intake, reduction in sodium intake and improved dietary habits as well as less traditional strategies targeting stress reduction and improving sleep hygiene can promote antihypertensive effects and may have a preventive role in the development of hypertension.[220,223,224,241] Proven lifestyle interventions such as these may add significant benefit to patients with resistant hypertension requiring multiple anti-hypertensive agents

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as was demonstrated in the recently published TRIUMPH trial. However the applicability of the trial results given the intensive interventions patients received in the trial and the prolonged effect of these interventions on patient outcomes are unknown.[242] Cancer guidelines around treatment and prevention of hypertension often mirror recommendations from general population guidelines with respect to lifestyle changes however it's important to appreciate the differences within cancer patient populations and acknowledge that recommendations need to be tailored to the patients current clinical status, prognosis and quality of life.[243]

For example the reduction in salt (sodium chloride; NaCl) intake has been a proven to reduce hypertension and its comorbid manifestations in the general population and is featured in the most recent hypertensive guidelines[244], most recent evidence has even shown that partial substitution of intake with potassium chloride (KCl) reduces cardiovascular disease risk and cerebral vascular events.[245]. However, this may not be appropriate in certain cancer patients such as those at risk of electrolyte imbalance and hyponatraemia from commonly used medications classes such as diuretics, ACE-Inhibitor/ Angiotensin-receptor blockers (ARB), antidepressants, and antipsychotics. Furthermore, several randomized controlled trials suggested that increasing cumulative exposure to ARBs may inadvertently increase the risk of cancer, specifically lung cancer.[246] Several chemotherapeutic agents have been causally associated syndrome of inappropriate anti-diuretic hormone (SIADH) such as vincristine, carboplatin, cisplatin and cyclophosphamide and more novel immunotherapy agents can seldom cause significant immune related complications such as colitis and adrenalitis resulting in gastrointestinal losses and adrenal insufficiency which can significantly disrupt sodium balance within the body.

Dietary lifestyle interventions have been shown to improve obesity rates in cancer patients and have a modest effect on improving quality of life.[247] However despite the crucial role of diet as a preventative lifestyle treatment for hypertension in the general population, and its proven role in lowering the risk of cancers such as CRC[248], evidence of diet interventions reducing hypertension in cancer populations is lagging.

CV fitness and exercise capacity are commonly reduced in cancer patients and there is strong evidence exercise/fitness training offers significant CV, cancer-related and general health benefits in cancer populations particularly in long term cancer survivors.[249–253] Exercise has been shown to decrease Reactive Oxygen Species (ROS) formation and both improve endothelial function whilst decreasing cardiac intracellular anthracycline levels.[254,255] It is plausible that exercise may cause a reduction in hypertension specifically, and more studies to ascertain this are crucial. Currently evidence for the positive impact exercise can have specifically on hypertension is drawn from non-cancer populations.[256] The American College of Sports Medicine have published a consensus statement regarding exercise safety for cancer patient groups including cancer survivors, confirming exercise's overall safety and efficacy.[257]

There is evidence for the use of cognitive behavioural therapies to promote lifestyle changes which can have a positive impact on hypertension in non-cancer patients[224], this may represent a novel strategy for the treatment of hypertension in cardio-oncology practice

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within the future as part of multidisciplinary approach to individualised management of hypertension.

Lifestyle factor modification is a dynamic process requiring lasting adherence and ongoing patient education and support. One method of addressing this with proven effectiveness will be with implementation of multi-disciplinary teams inclusive of both clinical practitioners, specialist nursing staff and allied health teams.[6,258]

Cancer therapy-related hypertension and its pharmacological management— Guidelines currently reflect that low dose combination antihypertensive medications are an appropriate starting point for hypertension in non-cancer patients. This has also been reflected in the QUARTET trial which found combination therapy superior to monotherapy treatments.[259] The recent publication of the STEP trial also demonstrated significant reductions in stroke, ACS and heart failure in the patients treated in the intensive therapy group.[260] Strategies such as these may also be true for cancer treatment-related hypertension by which there are multiple poorly defined pro-hypertensive driving mechanisms facilitating often difficult to control BP. However, caution must be given to multi-drug pharmacokinetic and pharmacodynamic interactions with cancer therapies and consideration for the higher risk of adverse events with more rigorous therapy in the cancer patient cohort.

An example of the difficulties faced when navigating clinical guidelines can be demonstrated with the choice of the initial antihypertensive pharmacological agent. Renin-angiotensin-aldosterone inhibitors may be preferred first line agents on the basis of their established efficacy in hypertension, primary and secondary prevention of CVD in general population, and an association between their use with significantly improved disease free survival outcomes in multiple malignancies[261], including breast, pancreatic, prostate, CRC and NSCLC, as well as in patients treated with immune-checkpoint inhibitors.[262] On the other hand, a recent study found that some HCC patients experienced tumour progression by ACE-inhibitor Captopril administration for the treatment of proteinuria caused by Apatinib.[263] A follow up study using tumour-bearing mouse models showed that the combination of ACE-inhibitor and anti-angiogenesis treatments may exacerbate the production of kidney-derived erythropoietin (EPO) and, in turn, reduce the anticancer efficacy of anti-angiogenesis treatments.[263]

With the rapid development and approval of many varying classes of cancer treatments with dynamic and often poorly understood mechanisms of actions, consideration of drug safety and important interactions when selecting anti-hypertensive therapy must routinely be considered. A well-documented adverse interaction is between non-dihydropyridine CCBs (verapamil and diltiazem) and sunitinib or sorafenib via CYP3A4 pathway inhibition.[264] The American Heart Association has recently published a guide for important pharmacokinetic drug interactions for hypertensive management in cancer patients, with many other relevant examples.[265]

The application of new emerging therapeutic options for the management of hypertension may also present both prospective beneficial treatment alternatives as well as challenges for individualised cancer therapy-related hypertension management in the future. More

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recently evidence from post hoc analysis of the PARAGON trial showed that the novel cardio-protective heart failure medication sacubitril/valsartan had a significant BP lowering effect in patients with defined resistant hypertension (patients optimised on three BP agents CCB, ARB and diuretic).[266] This is currently not reflected as a first line option in antihypertensive guidelines nor in patients without cardiac-failure and there is limited trail evidence for the use of these medications in cancer populations however given the relationship between many cancer therapies and the development of both hypertension and heart-failure and the evolving understanding of how treatment-related hypertension may proceed diastolic dysfunction and eventually heart-failure, treatment strategies such as these may play a pivotal role in the future of individualised antihypertensive management in this specific population group.

Similarly the adoption of interventional treatments such renal artery denervation (RDN) via thermal or chemical ablation to reduce sympathetic nervous activity around the renal arteries, which has evidence in non-cancer populations as a minimally invasive option for difficult to control arterial hypertension[267,268] could provide an abstract way to manage cancer treatment-related hypertension and circumnavigate issues with medication compliance, drug and therapy interactions and possible adverse effects for patients sensitive to effects of antihypertensive medications[269] however this would need to be a carefully individualised given associated risks with any interventional procedure and the lack of evidence in this area which is needed to guide future practice.

A lot of current uncertainties stem from limitations of clinical trials' data in cancer patients, which are often inadequately powered to assess screening protocols, devise optimal BP targets, and ideal hypertensive drug choice, and from challenges both logistically and economically of following patients for extended periods to document long-term risks and detailed outcomes to guide assessment and management in survivors. Compounding this issue is the variability in the reporting of lower grade hypertensive adverse events, which masks the true incidence within the trial population along with selection bias in trials which have historically excluded patients with pre-existing CVD and hypertension.[270,271] These issues may pose challenges for clinicians in deciding on the most appropriate management for their patients and may potentially lead to a hesitancy to treat hypertension, and instead adopt a more passive approach. This could in part explain a concerning report that over 60% of patients treated with ibrutinib, who were hypertensive at follow-up did not receive an increase or any additional BP medications.[272]

The consensus statement by the International Cardio-Oncology Society is an example of progress made to better adapt and modify recommendations for management of hypertension whilst incorporating CVD risk, BP thresholds for withholding anti-cancer treatment, and consideration of abrupt treatment-related hypertensive changes which may trigger initiation or escalation of treatment.[225] However, there remain inconsistencies between various guidelines and recommendations for optimal assessment and pharmacological management of hypertension, and there is growing need for large scale clinical trials to further guide optimal individualised cancer and therapy specific treatment pathways.[11,233] Jointly developed by the ESC, ICOS, EHA and ESTRO cardio-oncology

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guidelines published in 2022 provide evidence-based treatment framework for the cancer therapy-associated hypertension (Figure S2).[230]

Navigating the complexity of decisions around anti-hypertensive treatment selection with consideration of drug pharmacokinetics and pharmacodynamics, with the appreciation of both potential side effects and individual patient comorbidities requires a multidisciplinary approach and supports a shift in our practice of CVD management in cancer patients towards an "individualised approach" within the growing concept of onco-hypertension.[11,13,213,225]

Multidisciplinary models of care

In combination with established pharmacological treatment, a multidisciplinary approach to the treatment of hypertension in general population is now mandated in guidelines and is an accepted practice in many centres.[220,223,273–275] Multidisciplinary models of care have established efficacy in the management of a range of CVD including, hypertension, heart failure and atrial fibrillation,[276–279] as well as most forms of cancer.[280] These models of care have shown to be safe, improve patient care and clinical outcomes, improve quality of care, improvement medication adherence, and have shown to be cost effective.[281] Importantly, these teams can be embedded in a variety of settings including in hospital settings, outpatient clinics, home based care and now the emergence of telehealth options has increased post discharge follow up support.

The need for ongoing cardiovascular care in cancer patients is clear,[218,219,282] however the challenges of local availability of staff, differing geography, funding arrangements and different health systems, a "one size fits all approach" remains a challenge. Clearly defined, evidenced based care exists separately within CVD and cancer fields to assess, monitor and educate patients from diagnosis to long term follow up. There exists a great opportunity for merging these multidisciplinary models of care to enhance the immediate and long-term care of the cancer patients to improve their cardiovascular outcomes.

Ways to implement a multidisciplinary approach to preventative cardio-oncology whilst incorporating all of the patient lifestyle factors, risk factor screening, management and surveillance are poorly defined however technology such as artificial intelligence may provide an answer in the future to tackle these complex multifactorial issues and assist in development of validated patient screening tools and individualised treatment plans.[283]

Challenges and future directions

There remain notable gaps in our understanding of hypertension within cancer populations and the mechanisms by which cancer therapies promote hypertension. A significant proportion of cancer treatment-related data comes from oncological clinical trials designed to assess for anti-cancer drug efficacy and prognostic cancer outcomes: these trials have limited collection of CV data are not powered enough to detect a difference in the latter. This highlights a pressing need for larger, high-quality trials with a focus on specific CV outcomes such as hypertension dedicated trials of anti-hypertensive therapies in cancer patients and survivors, which in turn can inform clinical guidelines and recommendations for screening and management within this unique cohort. Additionally, as cancer patients

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are living longer and often pass the conclusion of important clinical trials, an opportunity is often lost to extract accurate data from long term cohorts to properly assess the hypertensive and CV risk and outcomes in these patients.

To gain a better mechanistic understanding of therapy related hypertension, we also need more and better preclinical models and studies which assess the underlying pathophysiological processes on a molecular, cellular and even genomic level.[284] We rely heavily on pre-clinical animal and cellular models to improve our understanding of these mechanisms. However, pre-clinical models are limited due to common overlapping risk factors for hypertension and cancer patients and accounting for this complexity is seldom possible.[285] Furthermore pre-clinical toxicity data for novel drugs is often extracted from in vivo and in vitro studies in the absence of cancer which does not replicate the important effect tumours may have on the development of hypertension as an adverse outcome.[19]

Genomic and transcription studies have highlighted we are in our infancy of understanding of the impact of variable gene expression within cancer populations and pharmacogenomic interactions between cancer treatments and antihypertensive therapies. Further studies assessing large patient cohorts may provide new insights on the underlying mechanisms and identify common signalling pathways (biosignatures) involved in the onset of hypertension in cancer patients. These biosignatures can then serve as potential targets and allow for discovery of blood-based biomarkers that may help prevent and predict adverse hypertension. These biomarkers would be also useful and beneficial for precision individualised management for cancer patients in the future.[283,286] The emergence of novel nanoparticle-based therapy may provide a platform in the future for cell based drug delivery and targeted gene expression modification.[287] Development of plasma therapeutic drug monitoring (TDM) for agents such as VEGF-TKI could potentially guide dose adjustment to reduce hypertensive adverse effects, however like many future projects requires more studies to assess application within clinical practice.[288]

Addressing the adverse cardiovascular outcomes of cancer treatment remains of critical importance in both the acute phase, and the survivorship phase. While development of and exploration of pre-clinical models and conduct of dedicated clinical trials is still some time away, in the interim we can focus on the delivery of best possible care that is within our knowledge. Implementing multidisciplinary models of joint cardiovascular and cancer care will help deliver more equitable care and improving both CV and cancer outcomes in cancer patients.

There are many opportunities that exist and can be taken advantage of to improve detection and management of hypertension and other CVD throughout patient’s journey (Figure 3). These require better communication and collaboration between cancer and cardiovascular clinicians, primary care providers, allied health pretensioners, and most important centred upon the needs of individual patients and their carers.

Overall, only though better integration of care, collaboration between researchers and clinicians, involvement of relevant stakeholders and breaking down silos of “cardiovascular”

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versus “cancer” care, can we achieve the ultimate goal of improving outcomes for our patients living with and beyond cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding

DTMN is supported by the National Heart Foundation Future Leader Fellowship (Award ID 104814), ALS is supported by the National Heart Foundation Future Leader Fellowships (Award ID 106025), TW is supported by the HNE Clinical and Health Service Research Fellowship. This work is supported in part by the NSW Health Cardiovascular Capacity Building Grant (ALS), Hunter Cancer Research Alliance New Strategic Initiatives Grant (TJH, DTMN and ALS), and John Hunter Charitable Trust Grants (TJH, TW, DTMN and ALS). S.M. Herrmann is supported by National Institutes of Health (NIH) Grant No. K08 DK118120 from the National Institute of Diabetes and Digestive and Kidney Diseases. J. Herrmann is supported by National Institutes of Health (NIH) Grant No. CA233610 from the National Cancer Institute.

Disclosures

ALS reports research grants from Biotronik, RACE Oncology, Bristol Myer Squibb, Novartis Australia, Roche Diagnostics, and Vifor; and consultancy fees/speaking honoraria from Novartis, Bayer, Bristol Myer Squibb, AstraZeneca, and Boehringer Ingelheim.

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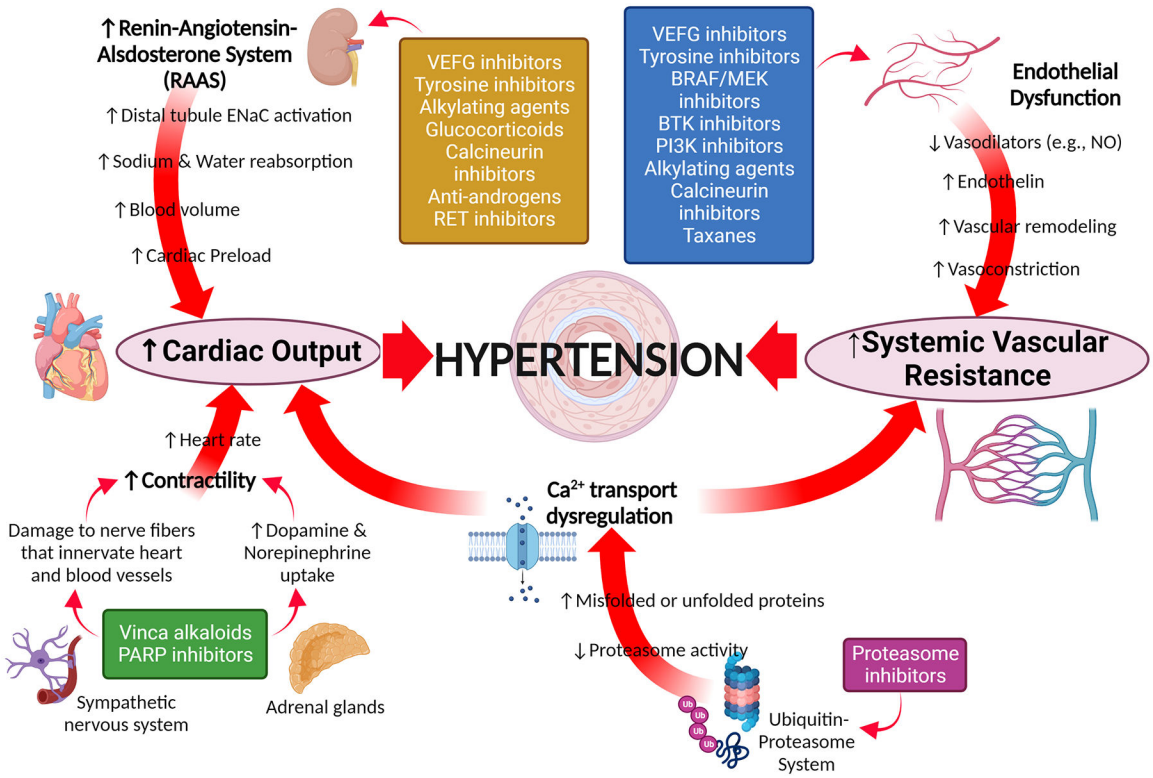

Figure 1. Pathophysiological changes associated with hypertension induced by new and emerging anti-cancer agents.

BRAF - B1 homolog v-raf murine sarcoma viral kinase oncogene; BTK - Bruton tyrosine kinase; ENaC -; MEK - mitogen-activated protein kinase; NO – nitric oxide; PARP - Poly(ADP-ribose) polymerases; PI3K - phosphatidylinositol 3-kinase; VEGF - Vascular endothelial growth factor.

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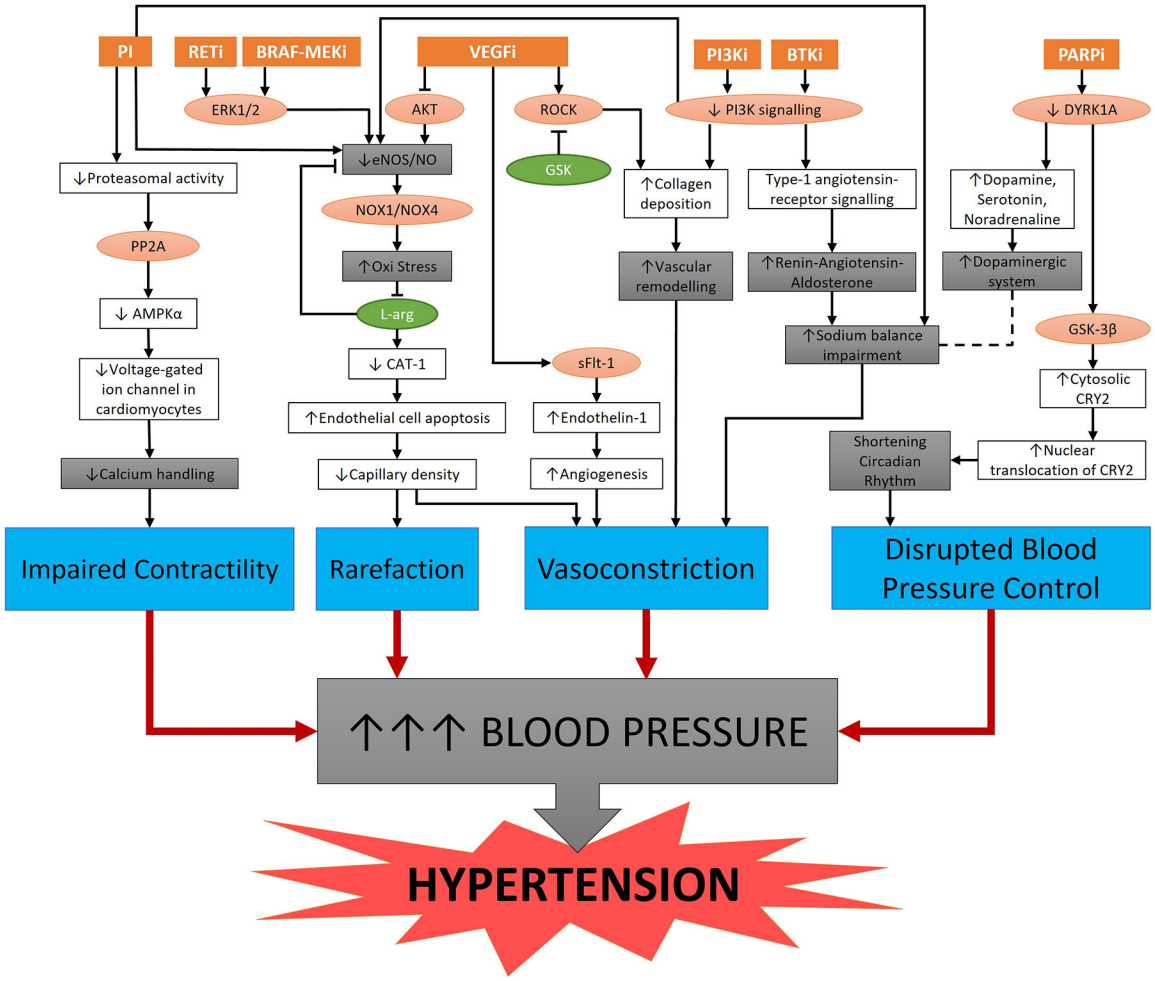

Figure 2. Potential mechanisms involved in the onset of hypertension by established and emerging cancer therapies.

Schematic representations of major pathways affected by cancer therapies (orange boxes): Proteasome inhibitors (PI), RET inhibitors (RETi), BRAF-MEK inhibitors (BRAF-MEKi), Vascular endothelial growth factor inhibitors (VEGFi), Phosphatidylinositol 3-kinase inhibitors (PI3Ki), Bruton tyrosine kinase inhibitors (BTKi), and Poly (ADP Ribose) Polymerase inhibitors (PARPi). Lines with arrowheads and flatheads at the end represent "activation" and "inhibition," respectively. Dashed line represents a plausible pathway. The red circles are key signalling molecules whilst green circles are potential anti-hypertensive therapeutic targets. The grey boxes represent the major mechanisms whilst the blue boxes indicate the common pathogenesis underpinning the onset of elevated blood pressure and, consequently, the development of hypertension. ERK = extracellular signal–regulated kinases; AKT = Protein Kinase B; ROCK = Rho-associated protein kinase; PI3K = Phosphoinositide 3-kinases; DYRK1A = Dual-specificity tyrosine phosphorylation-regulated kinase; eNOS = endothelial nitric oxide synthase; NO = nitric oxide; Y-27632 = ROCK Inhibitor; PP2A = Protein phosphatase 2; NOX = NADPH Oxidase; AMPKα = AMP-activated protein kinase; L-arg = L-arginine; GSK-3β = Glycogen synthase kinase-3 beta;

CAT-1 = Cationic amino acid transporter-1; sFlt-1 = Soluble fms-like tyrosine kinase-1; and CRY2 = Cryptochrome circadian regulator 2.

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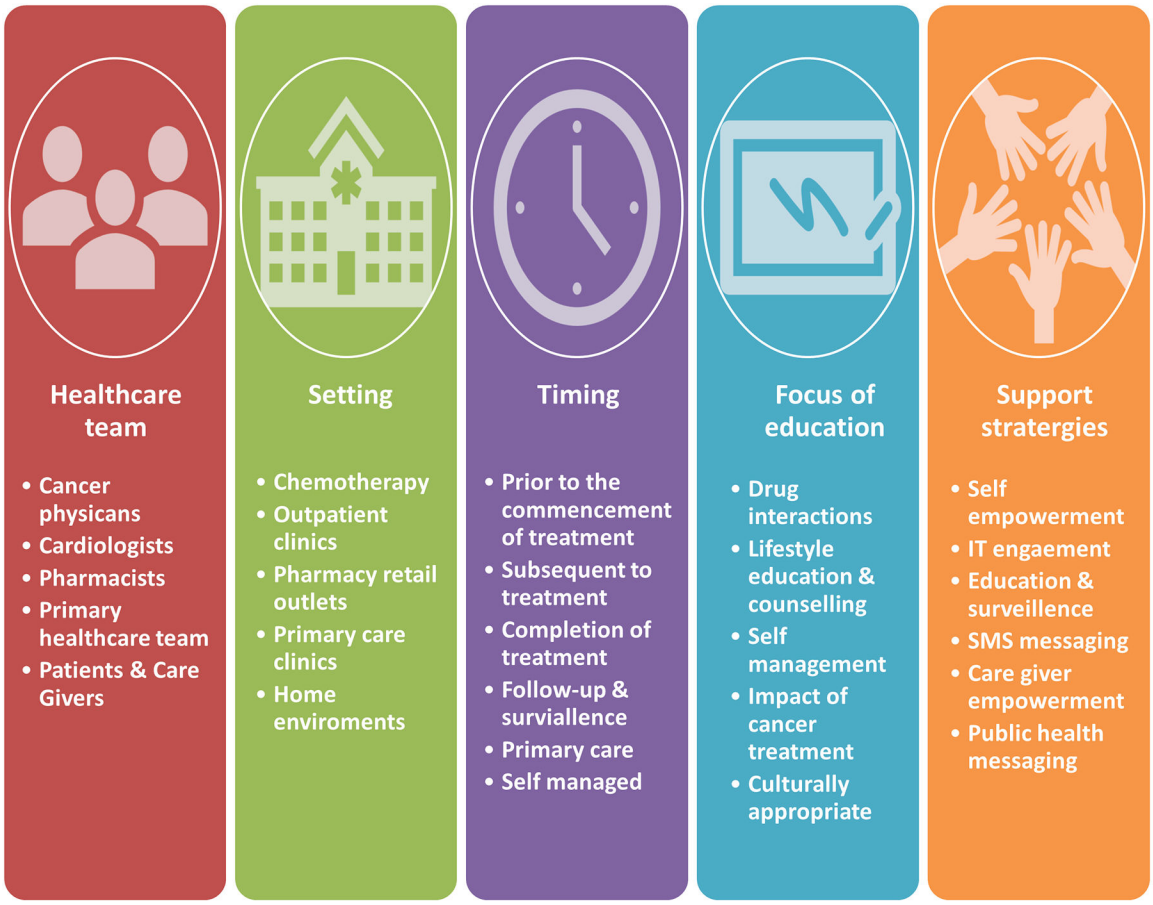

Figure 3.
Avenues for the detection and management of hypertension in cancer patients

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Table 1:

Overview of anti-cancer agents associated with development/exacerbation of hypertension

Class	Drug (Brand)	Mechanism(s)	Reference
VEGF inhibitors	Aflibercept Bevacizumab Ramucirumab	• Endothelial dysfunction • Decrease in NOS and prostacyclin I • Increase endothelin • Vascular remodelling • Capillary rarefaction • Decrease renal excretion of sodium	19,73–75,83
Tyrosine inhibitors	Axitinib Cabozantinib Cediranib Intedanib Lenvatinib Nintedanib Pazopanib Regorafenib Sorafenib Sunitinib Tivozanib Vandetanib Vatalanib	• Decrease in NOS activity • Activation of RAAS	13,19,73–75,80,84,289
Phosphatidylinositol 3-Kinase (PI3K) inhibitor	Alpelisib Copanlisib Duvelisib Idelalisib	• Increase vasoconstriction • Endothelial dysfunction	131,290
Burton tyrosine kinase inhibitors	Ibrutinib Acalabrutinib Zanubrutinib	• Decrease in HSP70 and PI3K signalling • Reduce VEGF • Vascular remodelling • Endothelial cell dysfunction	8,84,117,272,291
Alkylating agents	Cyclophosphamide Ifosfamide Busulfan Cisplatin	• Endothelial dysfunction • Arterial vasoconstriction • Increase intimal thickness • Abnormal vascular remodelling • Sodium retention • Nephrotoxicity	19,74,255,292
Immune checkpoint inhibitors	PD-1 inhibitors: Cemiplimab Nivolumab Pembrolizumab PD-L1 inhibitors: Atezolizumab Avelumab Durvalumab CTLA-4 inhibitors: Ipilimumab	• Reported to cause pulmonary arterial hypertension but mechanism is unclear Not associated in the short term with the initiation of hypertension	13,293–295
Vinca Alkaloids	Vincristine Vinblastine	• Cardiovascular autonomic neuropathy • Impairment in the vasodilator and contractile function	13,296,297
Glucocorticoids	Prednisone Methylpredisolone	• Increase sodium and water reabsorption	298

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Class	Drug (Brand)	Mechanism(s)	Reference
		• Increase sensitivity to vasoactive agents	
Calcineurin inhibitors	Cyclosporine Tacrolimus	• Increased proximal tubule sodium reabsorption • Renal dysfunction with distal tubule ENaC activation • Decrease in NO production • RAAS activation • Altered renal prostaglandin synthesis	299,300
Anti-androgens	Abiraterone Enzalutamide (mechanism unknown	• Increase mineralocorticoid activity (sodium and fluid retention)	8,301,302
Taxanes	Paclitaxel	• Endothelial dysfunction • Enhance toxicity of bevacizumab and anthracyclines	13,303

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Table 2:

FDA approved VEGF inhibitor anti-neoplastic therapies.

Drug (Type)	Target	FDA-approved Indications	References
Bevacizumab (IgG1)	• VEGF-A	• Cervical cancer • Ovarian epithelial • Fallopian tube • Renal cell carcinoma • Colorectal cancer • Glioblastoma • Non-small cell lung cancer	304,305
Sorafenib (TKI)	• VEGFR-2, −3 • PDGF receptor • RAF-1 • B-RAF	• Hepatocellular carcinoma • Renal cell carcinoma • Thyroid cancer	306–308
Lenalidomide (Immunomodulatory)	• VEGF • Cereblon	• Multiple myeloma • Mantle cell lymphoma • Follicular lymphoma	309
Sunitinib (TKI)	• VEGF receptor 1, −2, −3 • PDGF receptor α • PDGF receptor β • CSF-1 receptor	• Gastrointestinal stromal tumour • Pancreatic cancer • Renal cell carcinoma	310
Thalidomide (TKI)	• VEGF • FGF • Inhibition of phosphorylation of AKT pathway	• Multiple myeloma	311
Pazopanib (TKI)	• VEGF receptor • EGFR • Angiopoietin 1	• Medullary thyroid cancer • Renal cell carcinoma • Soft tissue sarcomas	74,312
Vandetanib (TKI)	• VEGF receptor • Angiopoietin 1	• Medullary thyroid cancer	313,314
Axitinib (TKI)	• VEGF receptor 1, −2, −3	• Renal cell carcinoma	315
Aflibercept (Fusion protein)	• VEGF-A • VEGF-B • PlGF	• Colorectal cancer • Macular degeneration	316
Regorafenib (TKI)	• VEGF receptor • PDGF receptor • FGF receptor	• Colorectal cancer • Gastrointestinal stromal tumours	317

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Drug (Type)	Target	FDA-approved Indications	References
	• c-Kit • RET • RAF-1	• Hepatocellular carcinoma	
Cabozantinib (TKI)	• VEGF receptor 2 • TIE-2	• Medullary thyroid cancer • Hepatocellular carcinoma • Renal cell carcinoma	74,318,319
Ponatinib (TKI)	• BCR-ABL • VEGFR • PDGFR • FGFR • EPH • c-KIT • RET • TIE2 • FLT3	• Chronic myeloid leukaemia • Philadelphia chromosome positive acute lymphatic leukaemia	74
Pomalidomide (TKI)	• VEGF • IL-6 • COX-2 • Cereblon	• Multiple myeloma	320
Ramucirumab (IgG1)	• VEGF receptor 2	• Colorectal cancer • Hepatocellular carcinoma • Stomach adenocarcinoma • Small cell lung cancer	321,322
Nintedanib (TKI)	• VEGF receptor • FGF receptor • PDGF receptor	• Idiopathic pulmonary fibrosis	323
Lenvatinib (TKI)	• VEGF receptor 1, −2, −3 • FGF receptor 1, −2, −3, −4 • PDGF receptor α	• Thyroid cancer • Endometrial carcinoma • Hepatocellular carcinoma • Renal cell carcinoma	324

EPH - Ephrin; FGF- Fibroblast growth factor; FLT3 - FMS-like tyrosine kinase 3; IL- Interleukin; PlGF- Placental growth factor; PDGF- Platelet derived growth factor; Tie-Tyrosine kinase receptor; VEGF-Vascular endothelial growth factor; RET – RET kinase (Adapted from[7,88]).

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TABLE 3:

Hypertension Incidence in major BRAF-MEK inhibitor trials adapted from Glen et al, 2022.[97]

Treatment and Cancer	Grade of AE and Hypertension Result	Study and References
Dabrafenib and trametinib (n=54) in metastatic melanoma BRAF V600 mutant.	All grade: 6% (7) Grade ≥ 3: 1% (1)	Flaherty et al, 2012.[325]
Dabrafenib and placebo (n=54) in metastatic melanoma BRAF V600 mutant.	All grade: 4% (2) Grade ≥3: 0	
Dabrafenib and Trametinib (n=211) unresectable stage IIIc or IV melanoma BRAF V600 mutant	All grade: 22% (46) Grade ≥3: 4% (8)	COMBI-d; Long et al, 2014.[326]
Dabrafenib and placebo (n=212) unresectable stage IIIc or IV melanoma BRAF V600 mutant	All grade: 14% (29) Grade ≥3: 5% (10)	
Dabrafenib and Trametinib (n=352) Metastatic melanoma BRAF V600 mutant	All grade: 26% (92) Grade ≥3: (14% (48)	COMBI-v; Robert et al, 2015.[327]
Vemurafenib (n=352) Metastatic melanoma BRAF V600 mutant	All grade: 24% (84) Grade ≥3: 9% (32)	
Dabrafenib and Trametinib (n=438) Stage III melanoma with resection and BRAF V600 mutant	All grade: 11% (49) Grade ≥3: 6% (25)	COMBI-AD; Long et al, 2017.[328]
Placebo (n=432) Stage III melanoma with resection and BRAF V600 mutant	All grade: 8% (35) Grade ≥3: 2% (8)	
Vemurafenib and cobimetinib (n=247) unresectable stage IIIc or IV melanoma BRAF V600 mutant	All grade: 16% (39) Grade ≥3: 6% (15)	CoBRIM; Ascierto et al, 2016.[329]
Vemurafenib and placebo (n=248) unresectable stage IIIc or IV melanoma BRAF V600 mutant	All grade: 8% (20) Grade ≥3: 3% (7)	
Encorafenib and Binimetinib (n=192) unresectable stage IIIc or IV melanoma BRAF V600 mutant	All grade: 11% (21) Grade ≥3: 6% (11)	COLUMBUS; Dummer et al, 2018.[330]
Encorafenib (n=194) unresectable stage IIIc or IV melanoma BRAF V600 mutant	All grade: 6% (11) Grade ≥3: 3% (6)	
Vemurafenib (n=191) unresectable stage IIIc or IV melanoma BRAF V600 mutant	All grade: 11% (21) Grade ≥3: 3% (6)	