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All about Hypertension and Prohypertensive Antineoplastic Treatment for Cancer Patients

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ABSTRACT
The prognosis for patients with a wide variety of malignancies has been improved by the introduction of a wide variety of innovative antineoplastic medicines, significantly increasing the number of cancer survivors. Cancer survivors are subjected to short- and long-term harmful cardiovascular side effects linked with anticancer therapy notwithstanding the oncological benefit. The most prevalent comorbidity among cancer patients, systemic hypertension, plays a significant role in the elevated risk of developing these unfavourable cardiovascular events. The risk factors for both cancer and hypertension are similar, their pathophysiological mechanisms are similar, and in some tumour forms, hypertension may also be a risk factor. There are several cancer treatments that raise blood pressure. Although some of the processes by which these anti-cancer drugs cause hypertension have been identified, further preclinical and clinical research is necessary to determine the precise pathophysiology and the best way to treat hypertension brought on by anti-cancer treatment. To reduce cardiovascular risks, hypertension can be better monitored and managed before, during, and after cancer therapy. This is crucial to guarantee that improvements in cancer survivability do not come at the price of rising cardiovascular toxicity and to maximise cardiovascular health in cancer patients and survivors.

I. INTRODUCTION

Chronically high blood pressure (BP) in the systemic arteries is the hallmark of systemic arterial hypertension, sometimes referred to as hypertension. The ratio of the systolic blood pressure (the force that the blood applies to the artery walls when the heart contracts) to the diastolic blood pressure is a typical way to represent blood pressure (the pressure when the heart relaxes). The BP thresholds that characterise hypertension vary on the technique of measurement (Table 1). [77]

Category	Subtype	Systolic BP (mmHg)	Diastolic BP (mmHg)
Office BP	NA	≥ 140	≥ 90
Office BP	Daytime (awake)	≥ 135	≥ 85
	Night time (asleep)	≥ 120	≥ 70
	24hr	≥ 130	≥ 80
Home BP	NA	≥ 135	≥ 85

Table 1 - Definitions of hypertension based on the 2013 ESH/ESC guidelines [77]. For the diagnosis of hypertension, systolic BP, diastolic BP or both have to exceed the reported values. (NA means Not Applicable)

The leading single cause of death and disability from all causes worldwide is hypertension, which is the most frequent preventable risk factor for cardiovascular disease (CVD; including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation, and peripheral artery disease), chronic kidney disease (CKD), and cognitive impairment [10]. Starting as low as 115/75 mmHg, far within the range that is regarded

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as normotensive, there is a graded and ongoing link between blood pressure and an increased risk of cardiovascular disease. Reduced disease load and increased lifespan among the global population are both largely dependent on effective hypertension prevention and treatment. As those with high CVD risk benefit most from BP lowering medication, it is crucial to take their projected atherosclerotic CVD (ASCVD) risk into account while treating hyperteinsion [11]. In this review we will discuss about the the epidemiology and pathophysiology of primary hypertension, strategies for delaying the progression of blood pressure elevation, management strategies (including optimal blood pressure targets) for lowering blood pressure and preventing CVD outcomes in patients with established hypertension, as well as prohypertensive antineoplastic therapies for Cancer Patients .

❖ Epidemiology

Prior to the development of industrial society, blood pressure levels had narrow distributions with mean values that fluctuated little with age and averaged around 115/75 mmHg [12], which is likely the typical (or optimal) blood pressure for humans. However, systolic blood pressure values consistently increase with age in both men and women in the majority of modern civilizations. This pervasive finding may be explained by the fact that age is a proxy for the likelihood and length of exposure to the many environmental factors, such as excessive sodium intake, inadequate potassium intake, overweight and obesity, alcohol use, and physical inactivity, that gradually raise blood pressure over time. Other variables that show minor but clear relationships with high BP levels in adulthood include genetic susceptibility and unfavourable intrauterine environments (such as pregnancy hypertension or pre-eclampsia) [13]. The absolute number of persons with hypertension increases significantly in response to even small changes in mean population blood pressure [14]. The prevalence of hypertension and its effects are highest among those with lower social level as economic development advances; this pattern is observed both within and between nations. At first, hypertension mostly affects people with high socioeconomic status. Furthermore, compared to earlier epidemiological transitions, the prevalence of hypertension has changed significantly more quickly between 2000 and 2010 [15].

- **Disease burden**

Currently, 874 million persons worldwide have systolic BP below 140 mmHg, whereas 3.5 billion adults throughout the world have non-optimal systolic BP values (defined as >110-115 mmHg). As a result, hypertension affects around one in four individuals [16]. Due to population growth, population ageing, and a 10% rise in the age-standardized incidence of hypertension, there was a global increase in the number of healthy life years lost to non-optimal BP of 43% between 1990 and 2015 [16]. According to the Global Burden of Illness research, non-optimal blood pressure continues to be the largest risk factor for disease and all-cause mortality worldwide, accounting for 9.4 million annual deaths and 212 million lost healthy years (8.5% of the total number of years lived in the world) [10].

- **CVD risk**

Both systolic and diastolic blood pressure are affected by the link between BP and CVD, whereas systolic blood pressure in adults is considerably more robust [19]. It is notable for all main CVD symptoms, including stroke (ischaemic and hemorrhagic), coronary artery disease, heart failure, peripheral vascular disease, and end-stage renal disease in both sexes, at all ages throughout adulthood. Level of BP has been shown to be a significant contributor to CVD risk in all prediction models, and the connection is independent of other CVD risk variables [21]. When they are 30 years old, around two-thirds of all persons with hypertension or using medication to control their blood pressure are at a 40% greater risk of having a cardiovascular disease (CVD) incident than their age- and sex-matched counterparts with lower blood pressure [18]. Additionally, CVD events likely to occur roughly five years earlier in people with hypertension than in people with lower blood pressure levels [18]. In people between the ages of 40 and 69, a 20 mmHg rise in systolic blood pressure or a 10 mmHg rise in diastolic blood pressure, regardless of baseline values, is linked to more than a doubling of the risk for stroke or ischaemic heart disease mortality [17], whereas a 5 mmHg drop in systolic blood pressure can reduce stroke mortality by 14% and CVD mortality by 9%. Although the absolute danger is much higher than it was earlier in life, the equivalent relative risk is significantly lower at older ages (≥80 years) [17].

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❖ **Pathophysiology**

- **BP regulation**

Blood volume, cardiac output (how much blood the heart pumps out each minute) , as well as the balance of arterial tone, which is influenced by both intravascular volume and neurohumoral systems, are all factors in determining blood pressure (discussed in the following sections). The renin-angiotensin-aldosterone system (RAAS), the involvement of natriuretic peptides and the endothelium, the sympathetic nervous system (SNS), and the immune system all play a part in the intricate interaction necessary to maintain physiological blood pressure levels. Any of these systems can experience dysfunction or disruption of variables that affect blood pressure management, which can eventually result in target organ damage (such as left ventricular hypertrophy and CKD) and CVD outcomes [22]. The complicated pathophysiological processes that lead to hypertension have hereditary roots. Multiple types of genes are involved in primary hypertension; some allelic variations of numerous genes are connected to an elevated risk of developing primary hypertension and are virtually always associated with a favourable family history. The development of hypertension is influenced by a variety of environmental variables, including high Na+ intake, poor sleep quality or sleep apnea, excessive alcohol use, and high mental stress [22,23,24]. Last but not least, as people age, their risk of getting hypertension increases due to the arterial vasculature's increasing stiffening, which is brought on by, among other things, gradually evolving alterations in vascular collagen and an increase in atherosclerosis [25,26,27]. When rheumatological infections like rheumatoid arthritis are present, immunological variables might also be very important. The diverse aetiology of hypertension is described by the mosaic hypothesis [28,29].

- **Sodium homeostasis regulation**

A key factor in controlling blood volume is sodium (Na+). High serum Na+ concentrations encourage fluid (water) retention, which raises blood volume and blood pressure. In normotensive people, compensatory hemodynamic adjustments take place to keep BP stable as dietary Na+ rises. These modifications include decreased renal and peripheral vascular resistance and enhanced endothelial production of nitric oxide, a vasodilator. However, if nitric oxide's impact is diminished or nonexistent, blood pressure rises. A risk factor for the development of salt sensitivity and eventual hypertension is endothelial dysfunction. Salt sensitivity is characterised by an increase in systolic blood pressure of at least 10 mmHg within a few hours of intake and is defined as a considerable increase in blood pressure after a Na+ load of ≥ 5 g. Individuals who are sensitive to salt have underlying endothelium dysfunction brought on by hereditary or environmental factors. These people often have an excess of transforming growth factor β (TGF-β) , which raises the risk of fibrosis and oxidative stress, and have low levels of bioavailable nitric oxide in response to a high salt load. Even salt-resistant people can acquire endothelial dysfunction due to chronic excessive salt intake, which also alters the gut flora and leads to changes that increase salt sensitivity and the onset of hypertension [30, 31]. Through the stimulation of T helper 17 (T_H17) cells, a high salt consumption also appears to promote autoimmunity [31]. Lactobacillus murinus levels in the gut microbiota of mice have been demonstrated to decrease with high salt consumption. By regulating T_H17 cells, L. murinus treatment of mice prevented salt from causing an aggravation of salt-sensitive hypertension [31]. According to these results, a moderate high-salt challenge in a human pilot research decreased the survival of Lactobacillus spp. in the intestine, increased the activity of T_H17 cells, and raised blood pressure [31]. As a result, the gut microbiota seems to have a role in the etiology of hypertension as well as the BP's salt sensitivity.

- **Renin-Angiotensin-Aldosterone System**

The RAAS regulates blood pressure in a variety of ways, including mediating Na+ retention, pressure natriuresis (the process by which increases in renal perfusion pressure (the gradient between renal arterial and venous blood pressure) cause decreased Na+ reabsorption and increased Na+ excretion), salt sensitivity, vasoconstriction, endothelial dysfunction, and vascular injury), as well as other factors that are crucial in the pathogenesis of hypertension [22]. The RAAS is present at the cellular level in numerous organs, but its most important function is to aid in the regulation of pressure-volume homeostasis in the kidney, where it keeps perfusion in volume depleted states (i.e., when there is a decrease in extracellular fluid volume as a result of sodium and fluid loss) and is suppressed in volume expanded (fluid overload) conditions. In the juxtaglomerular cells of the kidney, pro-renin and renin are

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produced, stored, and released in response to diverse stimuli. Renin's primary job is to break down angiotensinogen to create angiotensin I. The pathogenetic significance of the RAAS in hypertension is centred on the cleavage of angiotensin I by the enzyme angiotensin-converting enzyme (ACE), which produces angiotensin II. By boosting the activity of the sodium-hydrogen exchanger (NHE3), sodium-bicarbonate exchanger, and sodium-potassium ATPase, as well as by promoting aldosterone production and release from the adrenal glomerulosa, angiotensin II improves Na+ reabsorption in the proximal tubule [22]. Angiotensin II is also linked to endothelial dysfunction and causes renal, cardiac, and vascular damage. These effects are pro-fibrotic and pro-inflammatory and are mostly mediated by increased oxidative stress. These pathways directly link angiotensin II to hypertension-related target organ damage [22].

Due to its involvement in metabolising angiotensin II into angiotensin-1-7, angiotensin-converting enzyme 2 (ACE2) has become a key modulator in the pathogenesis of hypertension, CVD, and renal illness [33]. Angiotensin-1-7 inhibits the proliferation and development of vascular smooth muscle cells, cardiac myocytes and fibroblasts, glomerular and proximal tubular cells, as well as causes systemic and localised vasodilation, diuresis, and natriuresis [33]. Through signalling pathways that include mitogen-activated protein kinases (MAPK), PI3K-AKT, NADPH oxidase, TGF-β1, the EGF receptor, and NF-κB activity, angiotensin-1-7 also possesses cardiorenal protective effects that are mediated by the proto-oncogene Mas receptor [33,34,35]. Aldosterone is a key player in the development of hypertension because it activates the amiloride-sensitive sodium channel, also known as the epithelial sodium channel (ENaC), and stimulates renal Na+ reabsorption in the cortical collecting duct by binding to the mineralocorticoid receptor without directly altering gene expression.36 Additionally, aldosterone has a wide range of non-epithelial actions that support hypertension, vasoconstriction, and endothelial dysfunction [36,37]. These include vascular remodelling, fibrosis, extracellular matrix deposition in the blood vessels, and enhanced oxidative stress [36,37].

Hypertension As a Possible Risk Factor for Cancer

Although there are overlapping risk factors for hypertension and cancer, investigations on the direct connections between hypertension and incident cancer have been mainly inconsistent. [39,40] Several observational studies have suggested that hypertension is an independent risk factor for renal cell carcinoma (RCC). [39-42] Within the European Prospective Investigation into Cancer and Nutrition study population, one research of over 300,000 participants looked at the association between blood pressure, antihypertensive medication, and RCC. [43] individuals with systolic blood pressure (SBP) 160 mmHg or diastolic blood pressure (DBP) 100 mmHg had a 2.5-fold greater risk of developing RCC compared to individuals with SBP 120 mmHg or DBP 80 mmHg throughout a mean follow-up of 6.2 years. [43] Notably, a connection between antihypertensive medication and cancer was detected only when blood pressure was poorly managed, indicating that high blood pressure may predispose these people to developing RCC. Another possibility is that a complicating condition predisposes these people to both cancer and difficult-to-control hypertension. However, the link between hypertension and the occurrence of RCC was confirmed in a large population cohort research including over 10 million South Korean people. After an 8-year follow-up, hypertensive people had a higher incidence of RCC (20.9 versus 9.2 instances per 100 000 person-years, respectively), with an adjusted hazard ratio of 1.12. [41] Hypertension-induced chronic kidney disease, inflammation, and activation of oncogenic hypoxia-inducible factors and ROS are hypothesised to be the fundamental processes that predispose hypertensive persons to developing RCC. [41,42] Furthermore, other risk factors, such as obesity, may play a role in the development of RCC in addition to hypertension. [42,44] In contrast to RCC, the link between hypertension and the occurrence of other cancers is less evident. Several studies, notably in postmenopausal women, have revealed a relationship between hypertension and breast cancer. [39,45] A meta-analysis of 30 prospective studies found that hypertension was related with a 20% higher risk of breast cancer in postmenopausal women45, but this finding was not validated in a large Taiwanese population study involving 111 000 people. [46] There have also been hypothesised correlations between hypertension and colorectal, endometrial, prostate,

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etc hepatic carcinoma, however studies proving a definite causative association are missing. [39,47,48] Other studies, however, reveal that hypertension has little or no connection with various other cancer forms, including stomach, gallbladder, pancreatic, and lung cancer. [39,40,49,50]

Increased Cardiovascular Risk in Cancer Survivors

Improved cancer survival has shown a number of long-term negative cardiovascular consequences. [51] This has been especially noticeable in the case of juvenile cancer, with over 80% of children now living at least 5 years after a cancer diagnosis. [51] Notably, as compared to the general population, these childhood and adolescent cancer survivors have a 7-fold greater risk of cardiovascular death [52], and this heightened risk remains beyond the age of 50.53 CVD is also the main cause of morbidity and mortality in this cohort, with the exception of recurring cancer.[54] This elevated risk of CVD is also shown in adult-onset cancer survivors, according to a large registry investigation of 3.2 million cancer survivors in the United States. [55] CVD risk increases with age, and CVD overtakes breast cancer as the leading cause of death among older breast cancer survivors 10 years after diagnosis. [56]

The significant increase in CVD risk may be explained in part by the increased incidence of hypertension in cancer patients during treatment or who have survived in the medium to long term. Indeed, in a study of 3000 adult 10-year survivors of childhood cancer, the prevalence of hypertension topped 70% by the age of 50, which was 2.6-fold greater than would be predicted based on age, gender, race, and BMI-specific rates in the general population. [15] Furthermore, a retrospective investigation discovered that these survivors are more likely than their siblings to be prescribed hypertension medication. [57] This increased risk of developing hypertension, both in the short and long term, is most likely due to anticancer therapy. In a study of nearly 25 000 adult cancer patients in the United States, one-third acquired new-onset hypertension during follow-up, and anticancer medication was linked to a 2- to 3.5-fold higher risk of hypertension. [58] Furthermore, the large Childhood Cancer Survivor Study found that hypertension in cancer survivors increased the relative risk (RR) of cardiac events such as coronary artery disease (RR, 6.1), heart failure (RR, 19.4), valvular disease (RR, 13.6), and cardiac arrhythmias (RR, 6.0), independent of cancer therapy-related risk.16 It is worth noting that the probabilities of developing these significant cardiac events were considerably greater in survivors who had other cardiovascular risk factors or had undergone anthracyclines or chest irradiation. [16] A study of 23 000 5-year survivors from the same group validated these findings. [59] Fortunately, developments in cancer medicines and increased health surveillance programmes have lowered anticancer drug toxicities in children, improving their cardiovascular outcomes. [59] Nonetheless, hypertension remains a key driver of the elevated risk of cardiac events in cancer patients and survivors, where hypertension might be present or develop de novo after cancer treatment. [16, 60]

Anticancer Therapy and Hypertension

A wide range of anticancer drugs and adjuvant therapy used in oncology have been demonstrated to have prohypertensive effects, in addition to putative pathophysiological links between cancer and hypertension. The development of vascular endothelial growth factor inhibitors (VEGFI), which are linked with hypertension in a substantial proportion of treated persons, heightened public awareness of antineoplastic-induced hypertension [5]. Furthermore, several other regularly used antineoplastic medicines have been linked to a rise in blood pressure and either de novo or worsening of previously well-controlled hypertension. Patients with comorbidities such as cardiovascular disease and uncontrolled blood pressure are commonly excluded from oncological clinical trials. As a result, these data sources understate the real prevalence of hypertension and other cardiovascular toxicities.4,61-63 The majority of antineoplastic drugs' evidence for prohypertensive effects is generated mostly from observational and retrospective clinical research. Furthermore, the pathophysiological processes by which these chemicals cause an elevation in blood pressure are based mostly on findings from preclinical and in vitro investigations, rather than clinical studies or trials.

Vascular Endothelial Growth Factor Inhibitors

While the precise processes behind VEGFI's hypertensive effects are unknown, numerous molecular pathways have been hypothesised. A clinical research in which recombinant human VEGF was administered to individuals with coronary artery disease resulted in a quick drop in mean arterial pressure,114

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demonstrating that VEGF is a key regulator of vascular tone and blood pressure.115 Normally, VEGF stimulates vascular endothelial cells to produce NO and prostacyclin, two vasodilators, by stimulating eNOS (endothelial NO synthase) activity and cytosolic phospholipase A2-mediated arachidonic acid release, respectively.116,117 As a result, VEGFI reduces the bioavailability of these vasodilators.118,119 VEGFI, on the other hand, has been shown to significantly improve the bioavailability of vasoconstrictors, notably ET-1 (endothelin-1).69 As a result, there is an imbalance between vasodilators and vasoconstrictors that favours the latter. This increases vasomotor tone and leads to hypertension development. Polymorphisms in eNOS that are thought to reduce eNOS activity and hence plasma NO levels were linked to the development of high-grade hypertension following sunitinib treatment.120 This emphasises the need of maintaining a careful balance of vasoconstrictor and vasodilator variables. Interestingly, a preclinical investigation found that ET-1 receptor antagonists reduce the blood pressure rise caused by sunitinib. These medicines, however, are not yet licenced for the treatment of systemic hypertension in humans.121

Oxidative stress has been suggested as another key component to VEGFI's hypertensive effects by generating endothelial dysfunction, as seen by higher levels of ROS in VEGFI-treated rats.70,122 Surprisingly, new research suggests that the increase in ET-1-mediated vasopressor response and ROS production as a result of VEGFI-associated endothelial damage may be mediated by circulating endothelial nanoparticles.123 In a preclinical model, however, treatment of Tempol, a ROS scavenger, did not result in a significant reduction in the sunitinib-induced elevation in blood pressure.121 Microvascular rarefaction (a decrease in microvessel density), which leads to decreased microcirculation and higher vascular resistance, has been postulated to contribute to VEGFI-induced hypertension, given that patients taking VEGFI had a moderate degree of rarefaction.71 However, given the fast spike in blood pressure after starting medication and the rapid return to normal following VEGFI cessation, this rarefaction is most likely functional rather than structural. It's worth noting that VEGFI treatment has been linked to an increase in vascular stiffness. Sunitinib enhanced major artery stiffness within the first weeks of treatment in 84 patients with metastatic RCC, as evaluated by increased carotid-femoral pulse wave velocity.124 Another clinical investigation found an increase in vascular stiffness after 3 weeks of sorafenib therapy.125 Nonetheless, the precise contribution of vascular stiffness to VEGFI's prohypertensive actions is unknown, as it might be both a cause and a result of hypertension.125,126

It is worth noting that there is little evidence that the renin-angiotensin-aldosterone system (RAAS) has a role in VEGFI-associated hypertension. Indeed, earlier clinical investigations have shown that plasma renin levels drop after VEGFI medication, indicating that RAAS activity is inhibited.69,125 Furthermore, aldosterone levels remained unaltered throughout VEGFI therapy, despite the fact that hypertension developed in a patient who had previously undergone a bilateral adrenalectomy, indicating that aldosterone is not required for hypertension development in this scenario.125,127 Enalapril, an angiotensin-converting enzyme inhibitor (ACEI), could not prevent VEGFI-induced hypertension but did alleviate VEGFI-induced kidney damage in a preclinical trial.128 One retrospective study of patients with metastatic RCC engaged in anticancer treatment clinical trials found that individuals with hypertension treated with RAAS inhibitors outlived those treated with conventional antihypertensive medications.129 Although these findings are significant, they may be skewed due to treatment selection bias.

VEGFI-Induced Renal Toxicity

VEGF is essential for maintaining a healthy fenestrated endothelium in the renal glomerular apparatus, and VEGFI therapy can be nephrotoxic.131 According to Izzedine et al, there are two categories of VEGFI-induced renal events that can be separated based on the type of VEGFI treatment employed. Anti-VEGF-ligands (anti-VEGF monoclonal antibodies and soluble VEGF decoy receptors) were predominantly associated with thrombotic microangiopathy in a series of renal biopsies from patients with VEGFI-associated renal toxicity, whereas VEGF-TKI were predominantly associated with minimal change nephropathy and/or focal segmental glomerulosclerosis.132,133 These kidney toxicity may cause proteinuria as well as salt and water retention, which may contribute to the increase in blood pressure observed following VEGFI treatment.8 The unfavourable vascular and renal consequences of VEGFI have been dubbed a preeclampsia-like syndrome because they match the symptoms of the severe pregnancy

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complication preeclampsia.121 Preeclampsia is distinguished by hypertension, proteinuria, and elevated plasma levels of sFlt-1 (soluble fms-like tyrosine kinase-1), a VEGFR. As a result, VEGF bioavailability is considerably reduced in preeclamptic women, which is likely to play a key role in the disease's aetiology.134 Notably, aspirin, a cyclo-oxygenase inhibitor, is an effective preventative therapy for preeclampsia in high-risk women because it is hypothesised to restore the balance between vasoconstrictor and vasodilator components.135 In this situation, aspirin has the ability to reduce the negative effects of VEGFI treatment.

VEGFI-Induced Cardiac Toxicity

VEGFI treatment is also linked to left ventricular systolic dysfunction and heart failure.136,137 The clinical spectrum of VEGFI-associated cardiotoxicity varies from modest QTc-interval prolongation and asymptomatic left ventricular dysfunction to heart failure, cardiogenic shock, and death.138,139 One research used echocardiography and cardiac biomarkers to track 90 RCC patients who were on sunitinib.140 When compared to baseline, 10% of these individuals exhibited a 10% to 50% decrease in left ventricular ejection fraction, with the bulk of these changes happening within the first treatment cycle. Importantly, sunitinib dose reduction and/or antihypertensive drug therapy reversed at least some of the left ventricular dysfunction.140 VEGFI have the potential to have direct cardiac toxic effects, reducing the heart's ability to endure an increase in afterload caused by concomitant systemic hypertension.141 This emphasises the importance of good cardiovascular monitoring and blood pressure control prior to and throughout VEGFI treatment. A full summary of the processes driving VEGFI-associated cardiotoxicity has recently been published, which is beyond the scope of this article.142

Poly ADP Ribose Polymerase Inhibitors

PARP (poly ADP ribose polymerase) inhibitors such as olaparib, niraparib, rucaparib, and talazoparib have been licenced for treatment in breast and ovarian cancer by the US Food and Drug Administration.73 However, their effectiveness in pancreatic and biliary tract tumours, as well as glioblastoma, lung, and prostatic malignancies, has been investigated.143 PARP inhibitors bind to PARP1 and PARP2 at DNA damage sites, preventing other DNA repair proteins from being recruited. As a result, when tumour cell multiplication, DNA repair is blocked, and apoptosis and cell death occur.144 Only niraparib has been linked to hypertension in this medication class.73 In the NOVA study (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer), any-grade and grade 3 or 4 hypertension occurred in 19% and 8% of niraparib-treated patients, respectively,145 compared to 5% and 2% of placebo-treated individuals.145 Niraparib's prohypertensive effects could be due to an off-target effect: the FDA approval summary for niraparib states that it can bind to dopamine, norepinephrine, and serotonin transporters, inhibiting their cellular uptake, which is accompanied by niraparib's greater ability to penetrate the central nervous system than other PARP inhibitors.74 This has been postulated to contribute to the prohypertensive effects of niraparib, although it is still theoretical, and the mechanisms behind niraparib-induced hypertension are yet unknown.73 Several studies investigated the anticancer effects of combining PARP inhibitors with other anticancer drugs.146,147 When compared to PARP inhibition alone, the addition of VEGFI to PARP inhibition in patients with ovarian cancer showed favourable oncological outcomes, including extended progression-free survival.148,149 However, in the case of niraparib, this may raise the risk of hypertension. Indeed, in the phase 2 AVANOVA2 trial (Niraparib Plus Bevacizumab Versus Niraparib Alone for Platinum-Sensitive, Recurrent Ovarian Cancer), 56% of patients receiving niraparib plus the VEGFI bevacizumab developed hypertension, compared to 22% of patients receiving niraparib alone.149 Other PARP inhibitors, as previously stated, have not been linked to prohypertensive effects. Olaparib monotherapy was not related with the development of hypertension in 46 individuals with ovarian cancer.148 In fact, in the absence of confounding central effects, there is reasonable mechanistic evidence to suggest that these medicines may potentially have the ability to give heart and vascular protection. Indeed, PARP inhibitors have been shown in animal models, including hypertensive and diabetic mice, to prevent cardiomyocyte necrosis, reduce myocardial infarction size, and protect against vascular endothelial dysfunction.75,76 Interestingly, the PAOLA-1 study (Olaparib Plus Bevacizumab Versus Bevacizumab Alone Maintenance in Advanced Ovarian Cancer) of 806 patients found that the olaparib and bevacizumab combination

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group had a numerically lower incidence of hypertension (46% versus 60%) than the bevacizumab alone group.146 Although the idea that PARP inhibition might provide clinically relevant cardiovascular protection in cancer patients is fascinating, it has not been thoroughly examined.

Platinum-Based Compounds

Platinum-based drugs (cisplatin, carboplatin, oxaliplatin) are commonly used to treat malignancies of the testicles, ovaries, colon, bladder, and lungs, as well as mesothelioma.150 Their anticancer method includes platinum absorption in DNA, followed by production of apoptotic cell death via transcription inhibition.151 Although the stated frequency varies between studies, hypertension is prevalent after platinum-based treatment.152-154 In contrast to VEGFI-associated hypertension, platinum therapy-associated hypertension is a long-term impact that can arise years after treatment. This is particularly important in the case of testicular cancer, which has a high survival rate and is the most frequent malignancy among young men. One research of 1289 testicular cancer survivors found that 53% developed hypertension after receiving a cumulative dosage of more than 850 mg cisplatin during a median follow-up of 11 years, with an odds ratio of 2.3 compared to healthy controls.152 Other studies with follow-up periods ranging from 7 to 14 years found a prevalence of hypertension ranging from 14% to 39%.153,154 These findings indicate that hypertension develops and persists in a significant number of individuals after platinum-based treatment. It is worth noting that cisplatin may be detected in serum up to 13 years after initial exposure, suggesting that it might cause persistent endothelium activation. Indeed, greater circulating platinum levels have been linked to an increased risk of hypertension.77 Microalbuminuria (closely connected to endothelial dysfunction) was identified in 22% of individuals with a history of testicular cancer treated with cisplatin at least 10 years before.154

II. CONCLUSIONS

The introduction of innovative anticancer medicines has significantly improved the prognosis for individuals suffering from a wide range of cancers. Despite these positive results, several of these medications cause systemic hypertension during therapy, which might impede the safe administration of anticancer treatment. Furthermore, the rapidly rising population of cancer survivors is at higher risk of hypertension-related end-organ problems. While both cancer and hypertension have common risk factors and related pathophysiological pathways, the specific mechanisms behind the prohypertensive effects of emerging types of antineoplastic medicines remain unknown. Before, during, and after anticancer therapy, it is critical to carefully measure blood pressure, cardiovascular risk factors, and possible end-organ consequences. Specific guidelines for screening, monitoring, and treating hypertension in the general oncological community are currently absent, but they are highly necessary. In the day-to-day therapy of cancer and hypertension patients, a coordinated approach involving cardiologists, (hemato)-oncologists, and cardiovascular specialists remains critical. This collaborative strategy, which includes basic scientists, is critical for designing appropriate preclinical investigations and clinical trials for future directions to better steer these complex entangled difficulties. Only by doing so can the remarkable anticancer benefits of innovative and traditional medicines be maximised while cardiovascular danger is minimised.

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