Cancer Therapy-Related Hypertension

อภิชาต สุคนธสรรพ์

Disclosures

Research funding

Viatris for the " Thai CVD Screening Project "

Consultant & Honorarium

Pfizer Upjohn, Bayer, Boehringer Ingelheim, Sanofi Aventis, Abbott, Zuellig Pharma, Amgen, Menarini, Celltrion, DKSH, Novartis, AstraZeneca and Medtronic

Editor

The CMCC Journal Watch

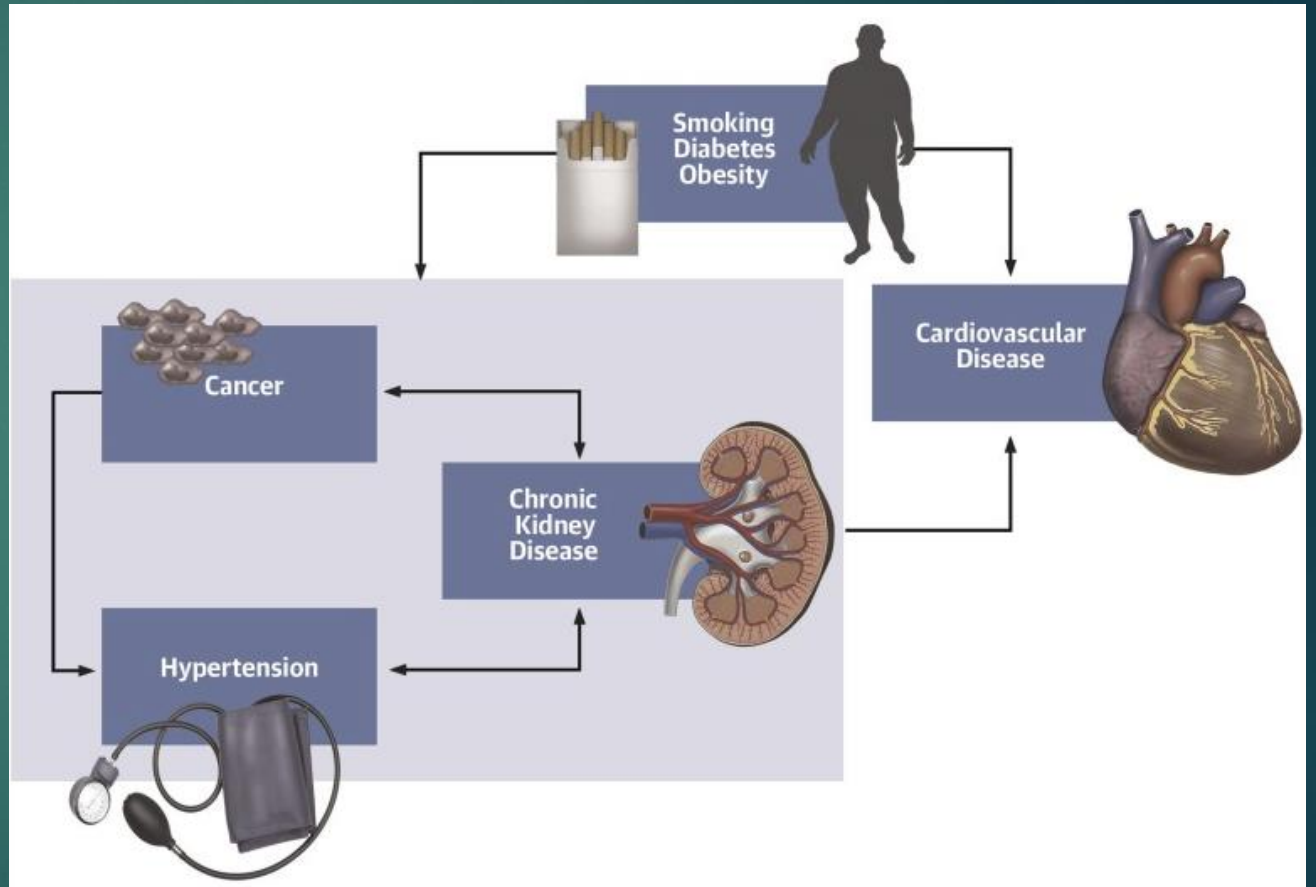
Hypertension Research

Epidemiology

- Cancer and CVD are major causes of morbidity and mortality globally.
- The prevalence of hypertension worldwide is increasing, reaching 1.3 billion in adults in 2019.
- The Global Cancer Observatory estimates that the number of new cancer cases worldwide will increase from 19.3 million in 2020 to >28 million in 2040.
- Hypertension is associated with an increased risk of cancer (Sci Rep 2019;9:8565).
- The prevalence of hypertension is higher in patients with cancer and cancer survivors than in the general population (J Clin Oncol 2013;31:3673-3680).
- CVD morbidity and mortality are increased in patients with cancer and cancer survivors.

Common Risk Factors of Hypertension and Cancer and Relationship between Cancer, Hypertension, and CVD

- Smoking, diabetes, chronic kidney disease, physical inactivity, obesity, oxidative stress, and inflammation are common in both hypertension and cancer.
- Many anticancer drugs cause BP elevation through numerous mechanism.



Cohen, J.B. et al. J Am Coll Cardiol CardioOnc. 2019;1(2):238-51.

Incidence of Hypertension Induced by Different Classes of Anticancer Drugs

กลุ่มยา	ตัวอย่างยา	ข้อบ่งชี้	อุบัติการณ์ของความดันสูง
VSPIs (VEGF Signaling Pathway Inhibitors)	Bevacizumab, Sorafenib, Ramucirumab etc	Renal, hepatocellular, thyroid, GI, stromal cancer	20-90%
BRAF/MEK inhibitors	Vemurafenib, etc	Melanoma, colorectal cancer	19.5%
Bruton TKIs (thyrosine kinase inhibitors)	Ibrutinib, etc	Chronic lymphocytic leukemia, mantle cell lymphoma	71%
RET-TKIs	Selpercatinib Pralsetinib	Thyroid, non-small cell Lung cancer	43% 21%
Poly (ADP-ribose) polymerase inhibitors	Niraparib	Breast, ovarian cancer	19%
Proteasome inhibitors	Carfilzomib, Bortezomib	Multiple myeloma	32% 10%

Incidence of Hypertension Induced by Different Classes of Anticancer Drugs (cont.)

กลุ่มยา	ตัวอย่างยา	ข้อบ่งชี้	อุบัติการณ์ของความดันสูง
Platinum-based compounds	Cisplatin, Carboplatin, etc	Mesothelioma, testicular, bladder, gynecological, colorectal, lung cancers	53%
Alkylating agents	Cyclophosphamide, Busulfan, Ifosfamide	Hematologic, solid organ malignacies	36%
Calcineurin inhibitors	Tacrolimus, Cyclosporin	After stem cell transplantation	30-60%
mTOR inhibitors	Everolimus, Sirolimus	Renal cell, breast, pancreatic neuroendocrine tumor	13%
Androgen receptor blockers	Enzalutamide	Metastatic prostate cancer	11%
Androgen synthesis inhibitors	Abiraterone Leuprolide	Metastatic prostate cancer, prostate cancer	26% 15%
Aromatase inhibitors	Anastrozole, etc	Breast cancer	8-13%

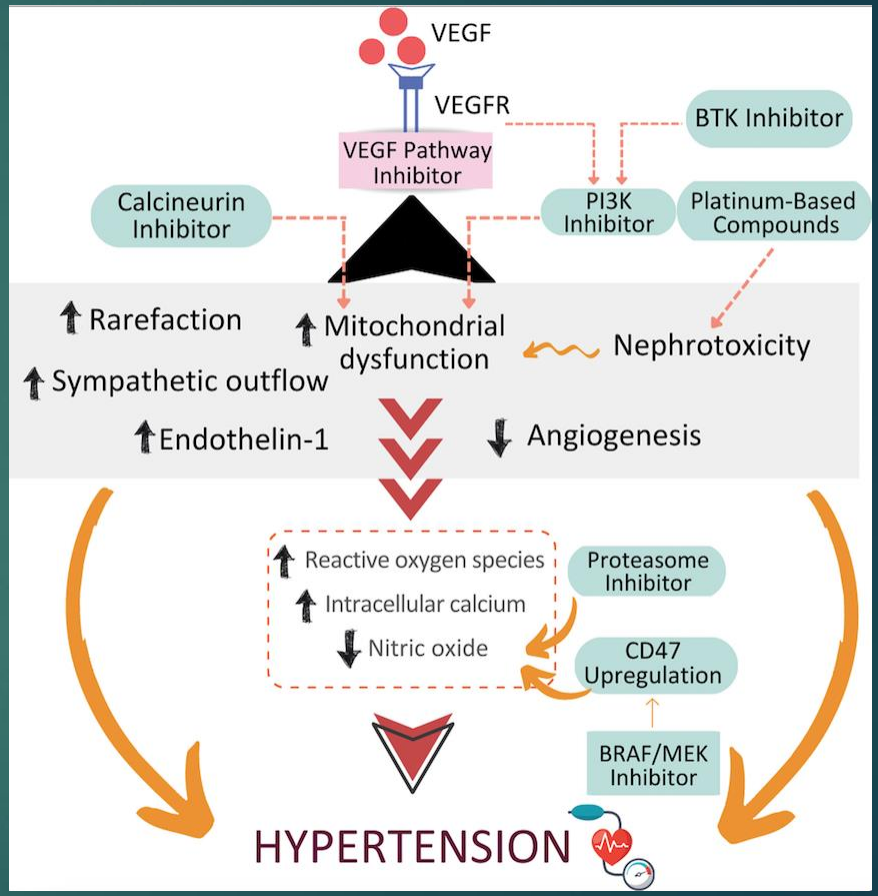
Putative Mechanism by which Anticancer Therapies cause Hypertension

Chemotherapeutic agents	Mechanism(s) of BP Elevation
Anti-VEGF and TKIs (thyrosine kinase inhibitors)	1. Increase vascular resistance by reduced NO production and reduced angiogenesis 2. Impaired natriuresis 3. Endothelin 1-mediated vasoconstriction 4. Thrombotic microangiopathy
Alkylating and alkyl-like agents Cyclophosphamide Ifosfamide Cisplatin	 Vascular endothelial injury Nephrotoxicity Nephrotoxicity and Vascular endothelial injury
Vinblastine	Vascular endothelial injury
Gemcitabine	Vascular endothelial injury Thrombotic microangiopathy
VEGF= Vascular endothelial growth factor	

Cohen JB, et al. JACC Cardiooncology 2019;1:238-51

Putative Mechanism by which Anticancer Therapies cause Hypertension

- Vascular Endothelial Growth Factor (VEGF) inhibition.
- Vascular and endothelium injury.
- Decrease NO, increase endothelin.
- Increase oxidative stress.
- RAAS and SNS stimulation.
- Renal injury leading to volume overloading.
- Decrease insulin sensitivity.



Adjunctive Therapies Used in Cancer Management That Can Increase BP

- Corticosteroids
- Exogeneous erythropoietin
- Non-Steroidal Anti-Inflammatory Drugs
- Calcineurin inhibitors

Putative Mechanism by which Adjunctive Therapies cause Hypertension

Adjuvant therapy	Mechanism(s) of BP Elevation
Erythropoietin stimulating agents	Increased erythrocyte mass Altered response to endogenous vasodilators and vasopressors
NSAIDs	Impaired natriuresis due to reduction in prostaglandin synthesis
Corticosteroids	Sodium retention due to mineralocorticoid receptor stimulation
Calcineurin inhibitors	Systemic and renal vasoconstriction

Cohen JB, et al. JACC Cardiooncology 2019;1:238-51

Putative Mechanism by which Adjunctive Therapies cause Hypertension

Radiation	Mechanism(s) of BP Elevation
Abdominal radiation	Renal artery stenosis
Head and neck radiation	Baroreflex failure

Cohen JB, et al. JACC Cardiooncology 2019;1:238-51

Definition of Hypertension in Patients with Cancer

IC-OS	Normal	Treatment threshold	Cancer therapy holding threshold	Exaggerated hypertensive response	Hypertensive emergency response
International Cardio-Oncology Society Definition	Not more than 130/80 mmHg	CVD/ ASCVD risk at least 10% : > 130/80 Otherwise : > 140/90	180/110 mmHg	SBP increase>20 mmHg	Very high BP associated with acute target organ damage requiring immediate BP reduction

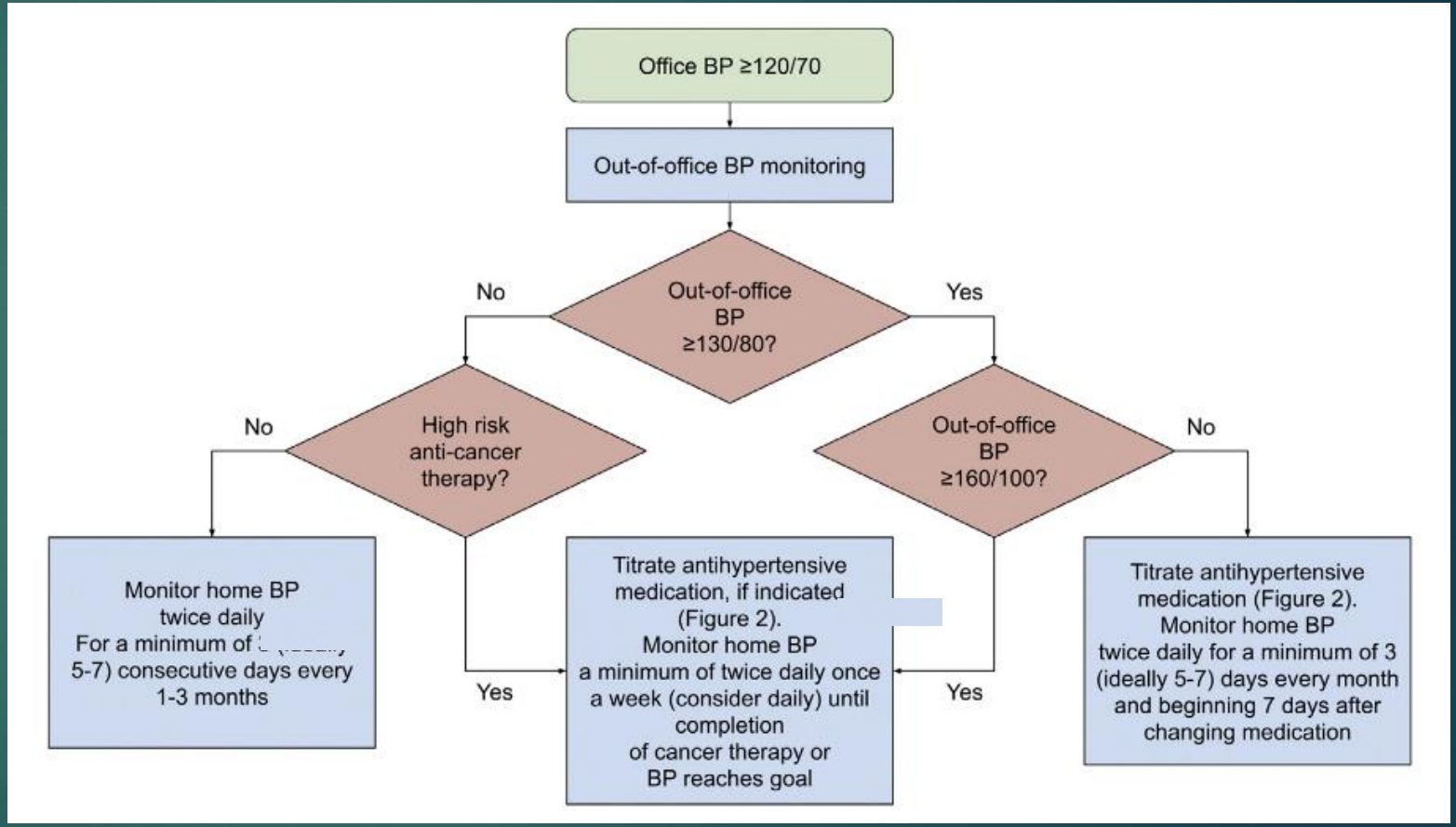
NCI	Grade 1	Grade 2	Grade 3	Grade 4
National Cancer Institute	120-139/80-89 mmHg	140-159/90-99 mmHg	From 160/100 mmHg	Life-threatening complications

Diagnosis

- Accurate measurement of BP is crucial for hypertension diagnosis and management, and special attention should be given to optimal control of pain and anxiety in patients with cancer. I B
- 24-hour ambulatory BP monitoring is recommend for diagnosis confirmation. I C
- Home BP monitoring should be used during treatment initiation or doses change especially in patients using VSPIs (vascular endothelial growth factor signaling pathway inhibitor) wherein worsening hypertension often occurs in days and can progress to hypertensive emergency. I C

Approach to Home BP monitor in cancer patients

High-risk anti-cancer therapies:
Anti-VEGF therapy,
Tyrosine kinase inhibitors,
Alkylating agents,
and High-dose corticosteroids



Cohen JB, et al. JACC Cardiooncology 2019;1:238-51

Before Cancer Therapy

- Standardized BP measurement
- Initiate lifestyle modification
- In patients with BP 180/110 or more, do not initiate anticancer therapy III C
- Start treatment if BP 130/80 or more if high CVD risk, otherwise if BP 140/90 or more
- Goal BP < 130/80 mmHg I C
- Optimize BP control prior to starting anti-cancer therapy

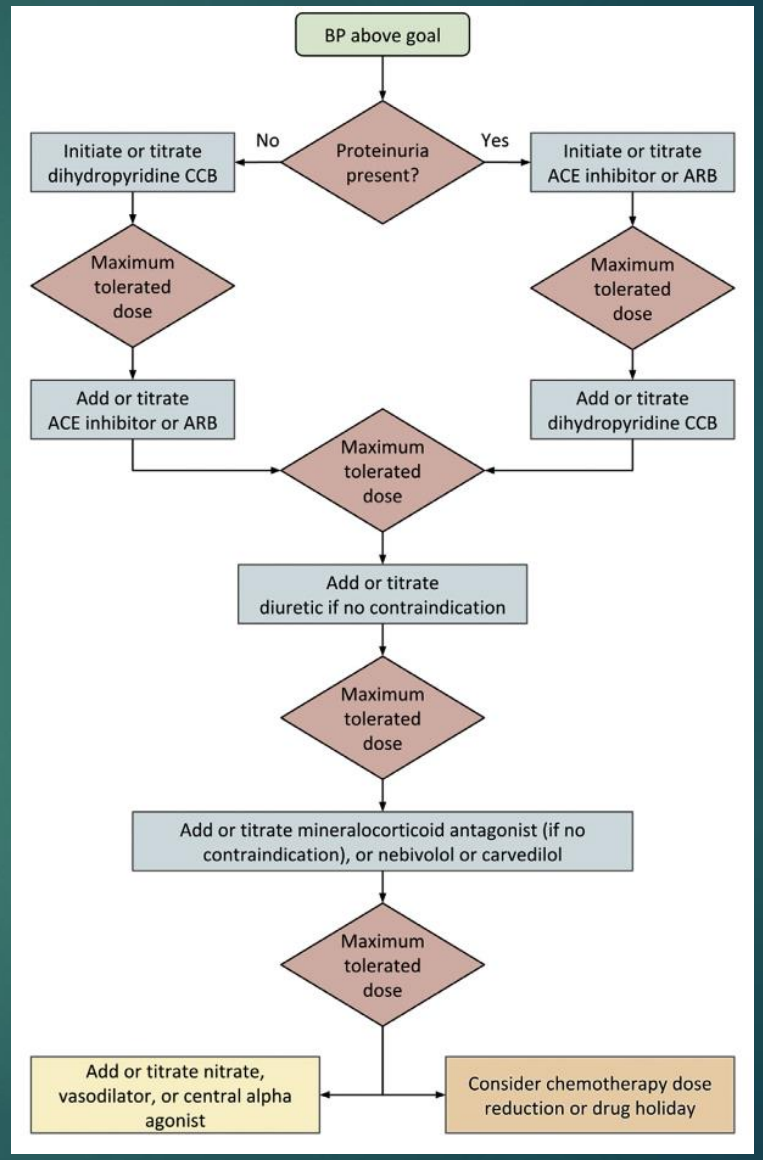
During Cancer Therapy

- Close BP monitoring and frequent medication adjustment if required
- First-line agents as general population
- Thiazide/Thiazide-like diuretics may be used only if needed, because unwanted effects including hypercalcemia in patients with bone metastasis, hypokalemia , hyponatremia, worsening of hypovolemic state II C
- Avoid non-DHP CCBs in patients treated with anticancer drugs that are susceptible to interactions mediated by CYP3A4 and/or P-gp III B
- Consider comorbidities (eg. diabetes mellitus, proteinuria, CKD, LVH) in selection of proper agents
- Hypertension induced by VEGF inhibitors may be treated with ACEis, ARBs, or DHP-CCBs II B
- Adequate management of pain and anxiety

ESH European Society of Hypertension ESH 1989 - 2019 30 YEARS

Approach to treating hypertension in patients receiving cancer therapy

- Step 1) Dihydropyridine CCB or ACEi or ARB
- Step 2) Two drugs or titrate
- Step 3) Add Diuretic
- Step 4) Add MRA or nebivolol or carvedilol
- Step 5) Add nitrate, vasodilator, or central alpha agonist
- Step 6) Chemotherapy dose reduction or drug holiday



Cohen JB, et al. JACC Cardiooncology 2019;1:238-51

After Cancer Therapy

- May need rapid reduction of antihypertensive therapy, shortly after stopping anti-cancer drugs, to avoid hypotension I C
- Close monitoring and look for anti-cancer drug-induced cardiovascular toxicity

Long-Term Management of Cancer Drug-Induced Hypertension

- Reduce antihypertensive treatment to avoid rebound hypotension
- Daily home monitoring may be necessary
- The prevalence of hypertension in cancer survivors is higher than in the general population, therefore close monitoring for the development of hypertension is required I C
- If required, treat as in general population

European Society of Hypertension

ESH 1989 - 2019 30 YEARS

Conclusions

- Many anticancer drugs and adjuvant therapies can raise blood pressure
- Cancer therapy-induced hypertension, especially that caused by VSPIs and proteasome inhibitors, is often reversible after discontinuation of these agents
- Hypertension control is essential before, during, and after completion of cancer treatment
- At least weekly BP monitoring is suggested for the first 4-8 weeks for patients on cancer drugs that increase BP and on discontinuation of these drugs
- Home BP monitoring should be encouraged
- Cancer survivors are at increased risk of hypertension and hypertension-associated complications such as AF, heart failure, CKD, necessitating a closer follow up for optimal management

ขอขอบคุณเป็นอย่างสูง และสวัสดี