Resistance to Antihypertensive Drugs Targeting Renin Angiotensin Aldosterone System in Cancer patients: A Case Series

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Short communication

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Abstract

Hypertension impacts overall prognosis in cancer patients. There are no specific recommendations for its management in these patients. We report a case series of 5 cancer patients with suboptimal BP lowering and even worsening BP with ACEi or ARBs that improved to normal upon discontinuation of these drugs.

Introduction

Hypertension is one of the most common comorbidities reported in cancer patients. Chemotherapeutic agents, especially vascular signaling pathway (VSP) inhibitors can not only worsen but cause de novo hypertension.[1] There are no specific recommendations for management of hypertension in cancer patients despite its significant impact on prognosis compared to any of the other cardiovascular risk factors in these patients.[2] Angiotensin-converting enzyme inhibitors (ACEi) are most commonly used to manage hypertension, especially in cancer patients receiving VSP inhibitors. However their efficacy in reducing blood pressure (BP) in these patients is not well explored. Dirix et al[3] reported that despite addition of an ACEi, the BP of a 51-year old male with renal cell carcinoma continued to increase up to 190/120mmHg until treated successfully with a long acting nitrate. Herein we present a case series of five cancer patients with uncontrolled hypertension while being managed with ACEi or Angiotensin Receptor Blockers (ARBs), which became controlled after discontinuation of these drugs. Baseline characteristics of these patients are indicated in **Table**. All 5 patients had laboratory workup in our cardio-oncology clinic, and had normal renal artery duplex scans.

Case 1

A 77-year-old African-American female with history of IgG-Kappa multiple myeloma presented for management of uncontrolled hypertension while being treated with bortezomib chemotherapy. Her BP log revealed systolic and diastolic blood pressure (SBP and DBP) ranges of 180-190mmHg and 70-80mmHg respectively, on an antihypertensive regimen including lisinopril 20mg daily, felodipine 10mg daily and spironolactone 25mg daily. Her BPs remained elevated and increased even further on higher dose lisinopril of 40mg daily. Lab data revealed elevated creatinine. After extensive workup, lisinopril was discontinued and carvedilol 12.5mg and hydralazine 25mg twice daily were added to her BP regimen. Her creatinine levels subsequently improved with improved BP readings ranging from 125-135/60-65mmHg (Figure).

Case 2

An 85-year-old Caucasian male with multiple cardiovascular comorbidities was treated with External Beam Radiation Therapy (EBRT) and adjuvant androgen deprivation therapy (ADT) for prostate cancer with multiple bone metastases. He presented to our cardio-oncology clinic for management of uncontrolled hypertension with SBP ranges of 140-150mmHg. His anti-hypertensive regimen included spironolactone 25mg daily, amlodipine 5mg daily and lisinopril 20mg daily. Amlodipine was discontinued due to significant lower extremity edema, and lisinopril was increased to 40mg daily. Subsequent 2-week BP log revealed increased SBP readings to a range of 150-160mmHg. Lisinopril was then discontinued and hydralazine was added to his BP regimen. At a dose of 50mg QID, his BP readings normalized to 125-135/70-80mmHg (Figure).

Case 3

A 79-year-old Caucasian female with Stage IIIC ovarian carcinosarcoma was referred for management of uncontrolled hypertension while on bevacizumab targeted therapy. Her BP was well controlled with spironolactone 25mg daily and metoprolol succinate 25mg BID. However due to concerns for bradycardia (HR 40-60 per min), metoprolol was discontinued. Following this, her SBP readings were slightly elevated in range of 140-150mmHg, so lisinopril 10mg daily was initiated. The patient's SBP remained elevated and in fact worsened, ranging from 160-180mmHg despite an increase in lisinopril dose to 20mg daily. Lisinopril was then discontinued, and her BP readings normalized to 120-130/60-80mmHg after re-initiation of low dose metoprolol succinate 25mg BID (Figure).

Case 4

A 65-year-old Caucasian female with history of stage IV ovarian cancer presented with uncontrolled BP since she began treatment with bevacizumab and cyclophosphamide. Her hypertension had been well managed on carvedilol 12.5mg BID prior to bevacizumab therapy, but she now had elevated BPs in the range of 160s/90s on this drug. Lisinopril 20mg daily was initiated for control of her bevacizumab-induced hypertension; but her BPs increased further, ranging from 170-180/85-115mmHg. Lisinopril was subsequently discontinued, and she was initiated on BP therapy with amlodipine 5mg daily. Following this change, her home BP readings significantly improved, with subsequent ranges of 120-140/80-90mmHg (Figure).

Case 5

A 72-year-old Caucasian female with history of breast cancer s/p surgery and intraoperative radiation therapy presented for management of uncontrolled hypertension while on cancer therapy with trastuzumab. Her SBP and DBP readings were found to be between 190-210 mmHg and 80-90 mmHg respectively on metoprolol 100mg daily, lisinopril 40mg daily, hydralazine 75mg TID, and chlorthalidone 25mg daily. Her antihypertensive regimen was adjusted to carvedilol 25mg BID, hydrochlorothiazide 25 mg daily, amlodipine 10mg daily and losartan 50 mg daily due to chronic cough on lisinopril. Losartan was later increased to 100 mg daily but BP remained elevated, and even worsened on this regimen (Figure). Losartan was finally switched to nifedipine 120mg daily; after which her BP readings declined to 120-140/70-80mmHg.

Discussion

Cancer therapeutic agents such as bevacizumab, sunitinib, sorafenib, etc. are known to increase BP by decreasing endothelial nitric oxide (NO) production due to VEGF inhibition.[4] In vivo studies have shown that ACEi increase release of NO, and are thus recommended as first line agents for management of anti-VEGF induced hypertension.[5] External beam radiation therapy also impairs endothelium-dependent vasodilation of conduit arteries, thus implicating a decrease in bioavailability of NO.[6] Androgen Deprivation Therapy is also associated with increased cardiovascular events.[7]

We observed resistance to antihypertensive agents targeting RAAS in our cancer patients, a phenomenon observed in African American patients treated with ACEi/ARB monotherapy for hypertension. 4 of our 5 patients were Caucasians and all had a history of hypertension prior to being initiated on chemotherapy. Their BPs

normalized once ACE-i/ARB was discontinued. All of these patients had normal renal artery duplex scans and secondary hypertension workup. Preclinical experiments in rats have shown an inability of ACEi to modulate higher increases in BP induced by VEGF inhibition, and suggest effectiveness in treatment for only mild increases in BP (10-15 mmHg).[8] They also observed reduced renin levels in the rats exposed to higher levels of cediranib (a potent VEGF signaling inhibitor), and thus concluded that RAAS gets downregulated to maintain normotension when exposed to these agents. Other preclinical studies have also shown suppression of RAAS by angiogenesis inhibition.[4] Thus, ACEi/ARBs which are suggested as first line for management of hypertension in cancer patients on VEGF inhibition therapy, may have suboptimal BP lowering effects in cases of severe hypertension.

No clinical evidence exists till date that favors one antihypertensive agent over the other in treating antiangiogenic therapy-induced hypertension. Nonetheless, Curwen *et al* demonstrated reversal of marked captopril-resistant hypertension induced by cediranib in rats after treatment with nifedipine.[8] Clinical studies have also shown effective BP management with these agents after treatment with bevacizumab.[9] Long acting nitrates that increase NO bioavailability have also been shown to effectively control hypertension in patients on antiangiogenic therapy that was refractory to ACEi and CCBs.[3] However, given the risk of compromising antiangiogenic benefits due to VEGF inhibition, it is prudent to use other available alternatives.

In conclusion, efficacy of drugs targeting RAAS for BP control in cancer patients on active therapy is still unclear, and further clinical studies evaluating the same are required.

Learning Points

- Hypertension is one of the most common comorbidities significantly impacting prognosis in cancer patients but still there are no specific recommendations for its management in these patients.
- Antihypertensive drugs targeting the Renin Angiotensin Aldosterone System (RAAS) are commonly used for management of hypertension in cancer patients. Preclinical studies in rats have demonstrated suboptimal blood pressure lowering effects of these agents in severe hypertension, however clinical experience with use of these agents for management of hypertension in cancer patients has never been reported.
- Our study involved 5 cancer patients with uncontrolled hypertension managed with Angiotensin-converting enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs) that later improved to normal upon discontinuation of these drugs.
- Since no clinical evidence exists till date that favors one antihypertensive agent over the other to treat antiangiogenic therapy-induced hypertension, clinical experience with use of antihypertensive agents for management of hypertension in cancer patients needs to be reported.

Abbreviations List

ACEi - Angiotensin-Converting Enzyme inhibitors

ARBs - Angiotensin Receptor Blockers

VSP - Vascular Signaling Pathway

RCC - Renal Cell Carcinoma

DM - Diabetes Mellitus

BP - Blood Pressure

SBP - Systolic Blood Pressure

DBP - Diastolic Blood Pressure

QID - 4 times daily

HR - Heart rate

PAI - Plasminogen activator inhibitor

NO - Nitric Oxide

RAAS - Renin Angiotensin Aldosterone System

VEGF - Vascular Endothelial Growth Factor

CCBs - Calcium channel blockers

Declarations

Ethics approval and consent to participate : Not applicable

Consent for publication : Patient's consent obtained

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Competing interests : The authors declare that they have no competing interests

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Authors' contributions : MG did literature search and had major contribution in writing the manuscript. RV helped in extraction of patient data and contributed in writing the manuscript. TO managed these patients and edited the entire manuscript.

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Table

Table. Baseline Characteristics of the Series Patients

Case	Age	Gender	Ethnicity	Cancer Type	Chemotherapy/ Radiotherapy	Initial BP Range*	Final BP Range**
1.	77	Female	African-American	Multiple Myeloma	Bortezomib	180-190/ 70-80	125-135/ 60-65
2.	85	Male	Caucasian	Prostate Cancer with multiple bone metastasis	Androgen deprivation therapy, External beam radiation therapy	140-150/ 70-80	125-135/ 70-80
3.	79	Female	Caucasian	Ovarian carcino-sarcoma	Bevacizumab	160-180/ 70-80	120-130/ 60-80
4.	65	Female	Caucasian	Ovarian cancer with metastasis	Bevacizumab and cyclophosphamide	160-170/ 90-100	120-140/ 80-90
5.	72	Female	Caucasian	Breast cancer	Trastuzumab	190-210/ 80-90	110-120/ 56-74

* Range of home blood pressure readings/log at presentation

** Final BP means range of home blood pressure readings/log when taken off ACEi and/or ARB

Abbreviations: ACEi – ace inhibitor; ARB – angiotensin receptor blocker

Figures

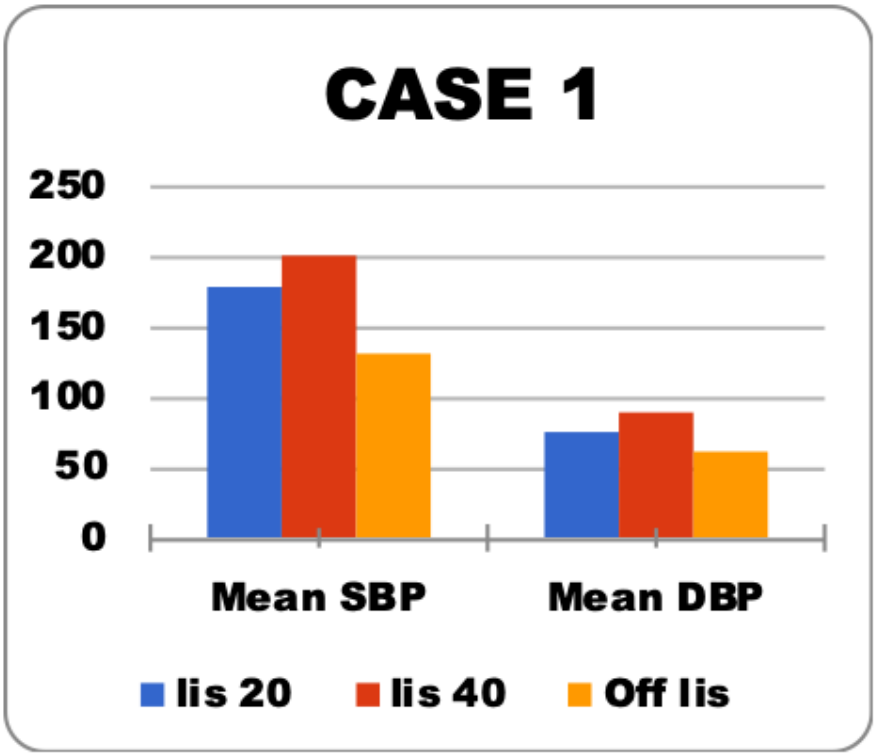

Figure 1

Comparison of average SBP and DBP readings in: 77 year-old female with multiple myeloma on chemotherapy with bortezomib. Graph shows SBP and DBP on low, high dose, and off ACEi therapy.

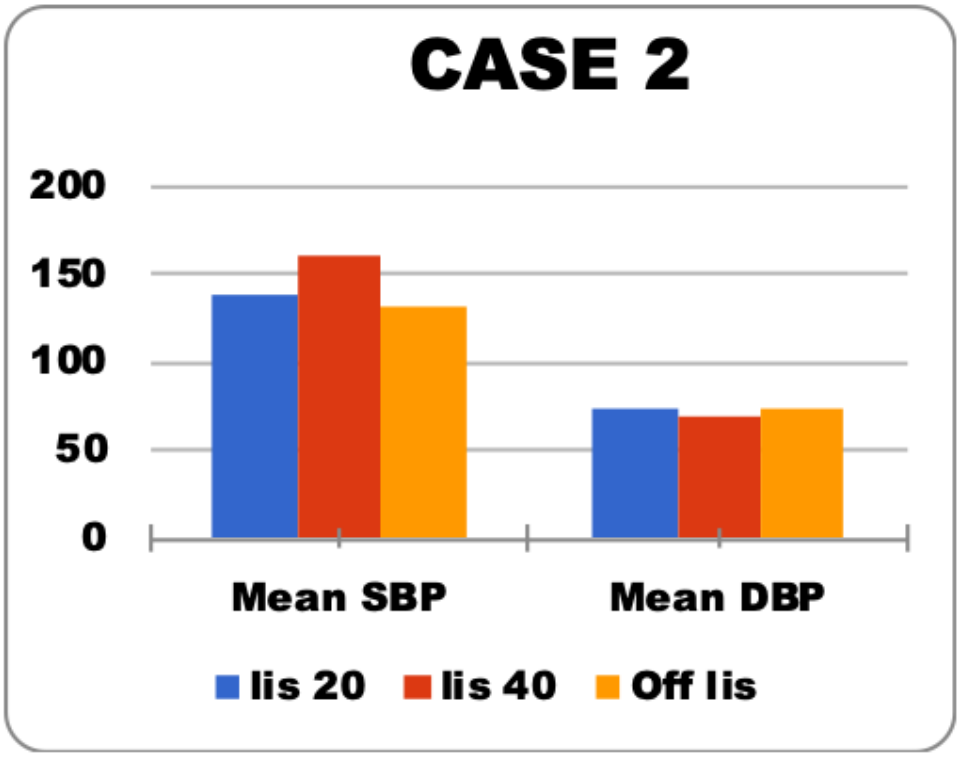

Figure 2

Comparison of average SBP and DBP readings in: 85 year-old male on ADT and EBRT for prostate cancer. Graph shows SBP and DBP on low, high dose, and off ACEi therapy.

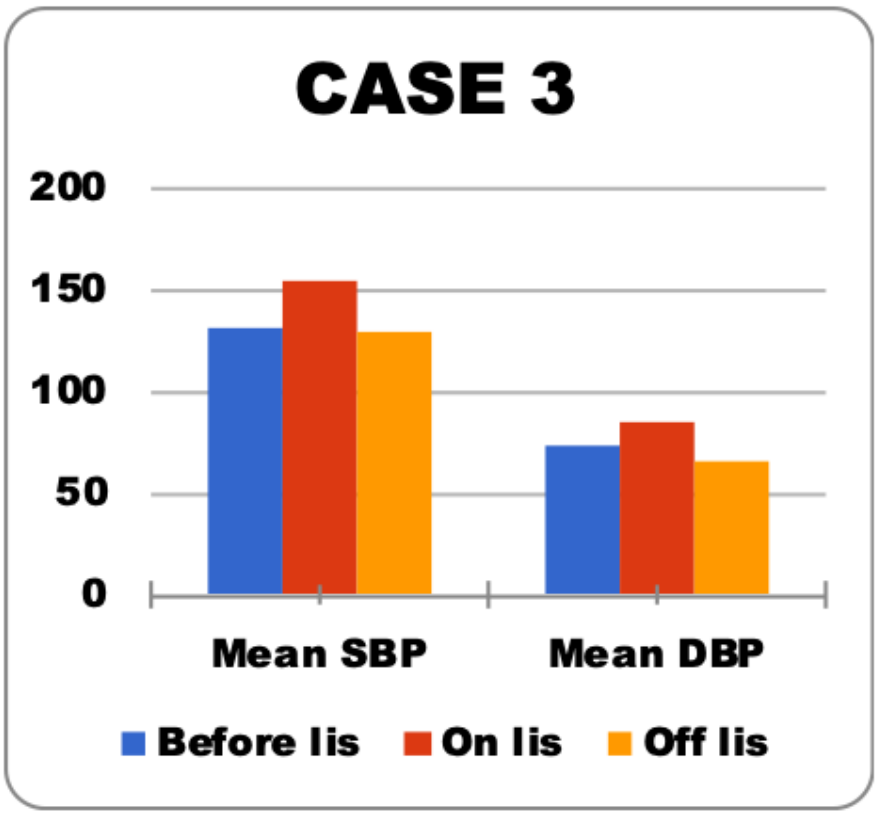

Figure 3

Comparison of average SBP and DBP readings in: 79 year-old female on bevacizumab immunotherapy for ovarian carcinosarcoma. Data shows SBP and DBP before and after starting ACEi therapy and after discontinuing it.

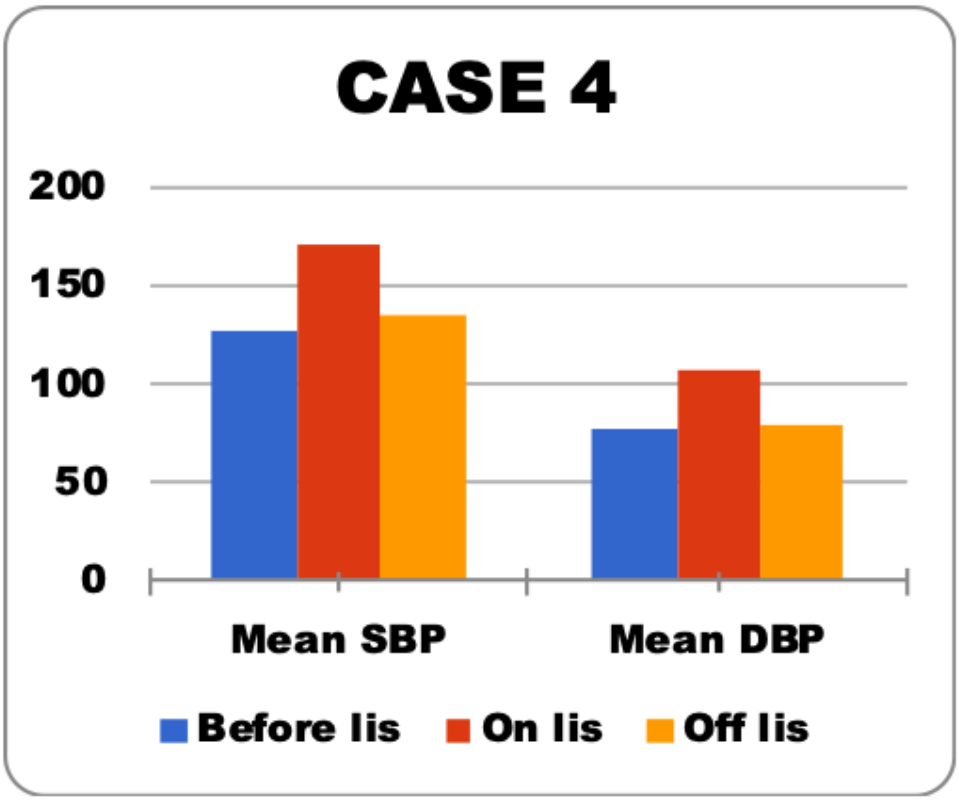

Figure 4

Comparison of average SBP and DBP readings in: 65 year-old female on chemotherapy with bevacizumab for ovarian cancer. Data shows SBP and DBP DBP before and after starting ACEi therapy and after discontinuing it.

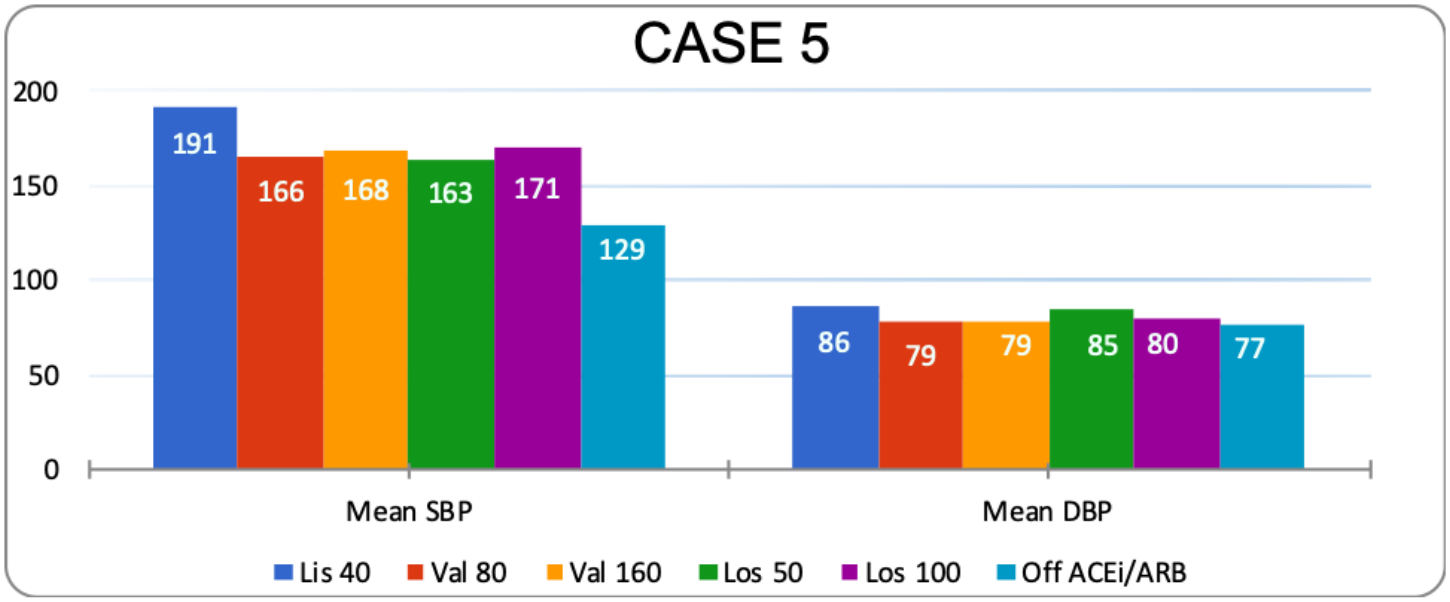

Figure 5

Comparison of average SBP and DBP readings in: 72 year-old female on cancer therapy with trastuzumab for breast cancer. Data shows SBP and DBP on and later off ACEi and ARB therapies.