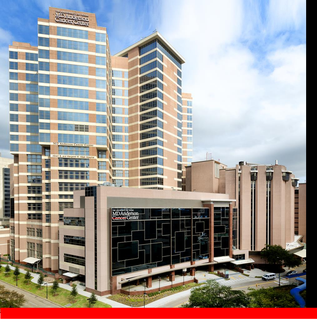

Prospective Study Evaluating Management of Hypertension Induced by anti-VEGF Therapy in Patients with Active Cancer: VEGFHTN Trial

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Background

- A growing number of anti-neoplastic agents target vascular endothelial growth factor (VEGF) signaling in various types of cancer. While generally well-tolerated, these agents are known to have cardiovascular toxicities, principally hypertension, with a reported incidence of 21-40% in first-time users.[1]
- Anti-VEGF therapy-induced hypertension can be challenging to control and significant enough to lead to a dose reduction or discontinuation of the VEGF-targeted therapy, preventing patients from completing their cancer therapy.
- A previously described novel blood pressure (BP) scoring system that incorporates both antihypertensive medication usage and blood pressure values has been shown to correlate with cancer progression.[2]

Objective

- To describe changes in a novel BP scoring method in patients with an antihypertensive algorithmic approach to managing anti-VEGF therapy-induced hypertension

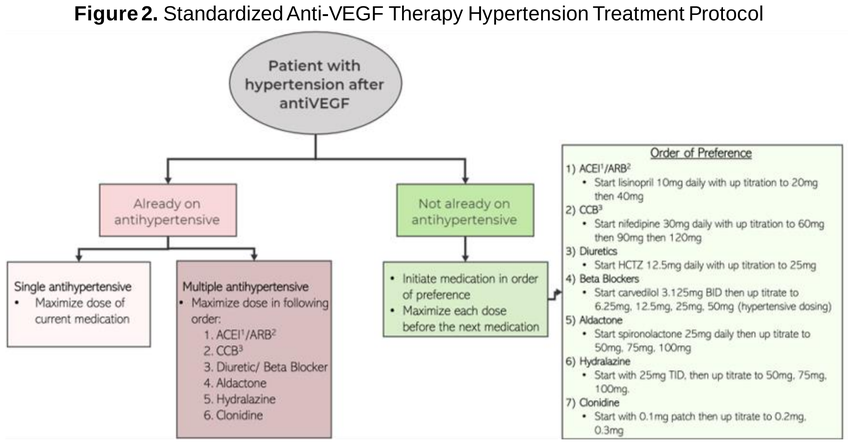
Methods

- A single-center prospective cohort of patients with cancer starting anti-VEGF therapy
- Anti-VEGF therapies included Axitinib, Bevacizumab, Cabozantinib, Lenvatinib, Ponatinib, Pazopanib, and investigational therapies with anti-VEGF activity.
- The novel BP scoring system was calculated for all patients as below and a subgroup analysis of patients that had 4-month BP follow-up was performed following the same methods as the original paper describing novel BP scoring.[2]
- Interval blood pressure data were collected, and antihypertensive medications were started per a standardized anti-VEGF therapy hypertension treatment algorithm (Figure 2).
- Hypertension was defined as consecutive blood pressure readings above 140/90 mmHg and controlled blood pressure as consecutive readings <140/90 mmHg.
- Time to development of hypertension, time to control of blood pressure, and the number of antihypertensive medications needed to control blood pressure were recorded.
- Statistical tests, including Pearson Chi-square and Fisher's exact tests, were used to compare variables between the prospective and retrospective cohorts. Survival analysis with Kaplan-Meier curves and log-rank tests were used to compare overall mortality.

Figure 1. Novel BP Scoring System Calculation

					Score of BP Medication
		SBP		DBP	
Total Score	Equals	0 = SBP < 140 mmHg 1 = SBP 140-159 mmHg 2 = SBP 160-179 mmHg 3 = SBP ≥ 180 mmHg		0 = DBP < 90 mmHg 1 = DBP 90-99 mmHg 2 = DBP 100-109 mmHg 3 = DBP ≥ 110 mmHg	+ 0 = No medication 1 = One medication 2 = Increasing dose of same medication or adding diuretics 3 = Two medications other than diuretics 4 = Three or more medications

Figure 2. Standardized Anti-VEGF Therapy Hypertension Treatment Protocol



1. Angiotensin-Converting Enzyme Inhibitor; 2. Angiotensin II Receptor Blocker; 3. Calcium Channel Blocker

Results

- A total of 169 patients were enrolled in this cohort study and 153 patients had data available for evaluation with 88 patient being included in the subgroup with 4-month follow-up novel BP scoring (Figure 3)

Figure 3. Consort Flow Diagram

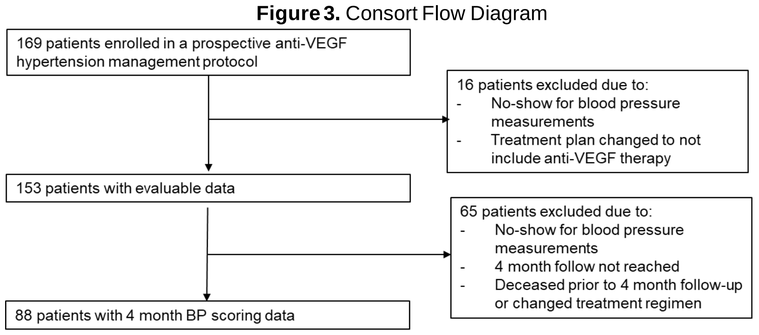
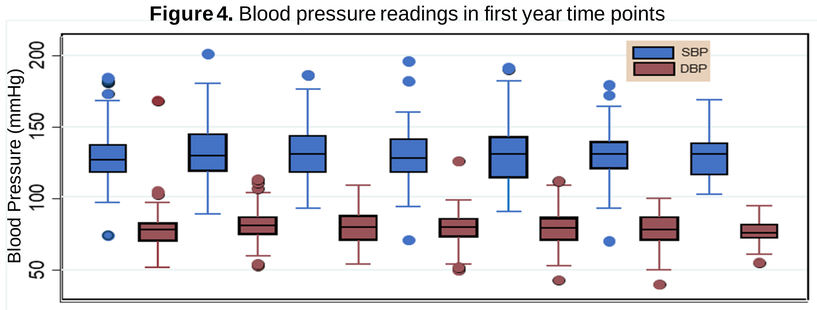


Table 1. Demographic and Clinical Characteristics of Patients Receiving Anti-VEGF Therapy in the total cohort and the 4 month follow-up cohort

Characteristic	Total Cohort (n=153)	4-month Cohort (n=88)
Age, years (Mean ± SD)	61.2 ± 11.6	62.3 ± 12.0
Female, n (%)	74 (48.4)	36 (40.9)
Race/Ethnicity, n (%)		
Hispanic, White	19 (12.4)	15 (17.1)
Non-Hispanic, Black	8 (5.2)	4 (4.6)
Non-Hispanic, White	124 (81.1)	67 (76.1)
Other	2 (1.3)	2 (2.3)
Comorbidities, n (%)		
Smoking		
Active	11 (7.3)	6 (6.9)
Former	52 (34.4)	33 (37.9)
Never	88 (58.3)	48 (55.2)
CAD	10 (6.5)	7 (8.0)
HFrEF[1]	1 (0.7)	1 (1.1)
HFpEF[2]	1 (0.7)	1 (1.1)
Hypertension	99 (64.7)	61 (69.3)
Hyperlipidemia	42 (27.5)	31 (35.2)
Diabetes Mellitus	39 (25.5)	21 (23.9)
Atrial Fibrillation	7 (4.6)	5 (5.7)
Prior Radiotherapy	70 (45.8)	37 (42.1)
Prior Chemotherapy	109 (71.2)	63 (71.6)
Hypothyroidism	50 (32.7)	
Cancer Type, n (%)		
Breast	17 (11.7)	7 (8.3)
Colorectal	12 (8.3)	4 (4.8)
HCC[3]	26 (17.9)	19 (22.6)
Prostate	14 (9.7)	9 (10.7)
RCC[4]	31 (21.4)	20 (23.8)
Other[5]	45 (31.0)	25 (29.8)
Cancer therapy, n (%)		
Axitinib	11 (7.2)	7 (8.0)
Bevacizumab	21 (13.7)	18 (20.5)
Cabozantinib	12 (7.8)	7 (8.0)
Lenvatinib	19 (12.4)	12 (13.6)
Ponatinib	1 (0.7)	1 (1.1)
Pozapanib	1 (0.7)	1 (1.1)
Sitravatinib	2 (1.3)	2 (2.3)
Investigational anti-VEGF[6]	71 (46.4)	35 (39.8)

1. Heart failure with Reduced Ejection Fraction; 2. Heart Failure with Preserved Ejection Fraction; 3. Hepatocellular Carcinoma; 4. Renal Cell Carcinoma; 5. Bladder, Esophagus, Fallopian Tube, Head and Neck, Lung, Musculoskeletal, Other, Ovarian, Pancreas, Parotid Gland, Skin, Testes, Thyroid; 6. Experimental Anti-VEGF therapies in Phase I studies

Figure 4. Blood pressure readings in first year time points



Number of patients	153	128	117	103	88	96	41

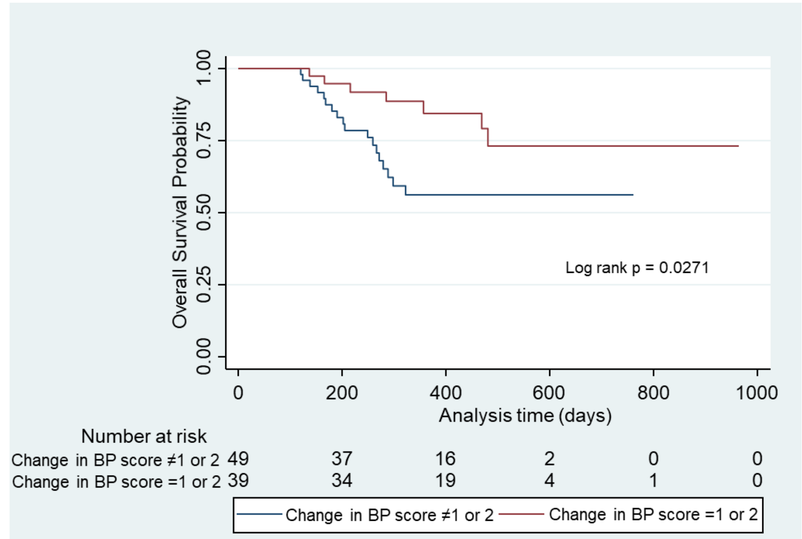
Results (Cont.)

Table 2. Comparison of novel BP scores and hypertension development, antihypertensive medications, and Anti-VEGF Cancer therapy interruption for patients in the cohorts

	Total Cohort (n=153)	4-month Cohort (n=88)
Hypertension Developed, n (%)	135 (88.2)	78 (88.6)
Pre anti-VEGF Novel BP Score, mean ± SD	1.65 ± 1.64	1.84 ± 1.60
4 month anti-VEGF Novel BP score, mean ± SD	-	3.35 ± 1.63
Change in Novel BP score, mean ± SD	-	1.51 ± 1.72

- The majority of patients in both cohorts developed hypertension while on anti-VEGF therapy
- The novel BP score increased by 1.51 on average in the 4-month cohort population
- No statistically significant differences in systolic or diastolic blood pressures were observed between time points (Figure 4)
- Patients who had increases of 1 or 2 in the novel BP score had improved overall survival to those who did not have increases or those with increases in the BP score of ≥ 3 (Figure 5)

Figure 5. Kaplan-Meier Overall Mortality by Change in BP Score



Conclusions

- A significant proportion of patients receiving VEGF-targeted therapy will develop hypertension
- No statistically significant differences were noted systolic or diastolic blood pressures after starting anti-VEGF therapy however the increase in the novel BP score by the BP scoring system which incorporates antihypertensive medication changes was observed
- Patients in a narrow window of increase in novel BP score (1- or 2-point increase) were found to have improved overall survival
- Further studies are needed to validate the use of a novel BP scoring system in patients with anti-VEGF induced hypertension

Limitations

- Small sample size limits the ability to assess differences in outcomes the effects of individual antihypertensives and their effectiveness on blood pressure control in the setting of anti-VEGF related hypertension
- There is a selection bias present in the prospective cohort in that patients enrolled are more likely to develop hypertension.

References

1) Wasserstrum, Y., Kornowski, R., Raanani, P. *et al.* Hypertension in cancer patients treated with anti-angiogenic based regimens. *Cardio-Oncology* **1,** 6 (2015). https://doi.org/10.1186/s40959-015-0009-4

2) Bilen MA, Durand JB, McQuinn L, et al. Evaluation of a novel blood pressure scoring method and its association with clinical response in cancer patients treated with anti-vascular endothelial growth factor therapy. Invest New Drugs. 2014 Aug;32(4):717-22. doi: 10.1007/s10637-014-0104-7. Epub 2014 Apr 26. PMID: 24764123.