Severe Refractory Pulmonary Hypertension Linked To Bevacizumab In A Patient Treated For Metastatic Ovarian Cancer

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Introduction

Bevacizumab is a recombinant humanized monoclonal antibody used in multiple cancers to prevent angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A) [1]. The drug was initially approved for colorectal cancer treatment and has since been used in treating ovarian, lung, renal, and neuronal cancers [2]. Common side effects of bevacizumab include hypertension, arterial thromboembolism, and bleeding, with an FDA warning for increased risk of gastrointestinal perforations [3].
However, the development of pulmonary arterial hypertension (PAH) is an exceedingly rare side effect with only a handful of cases [4].
There are currently no guidelines for screening except for routine laboratory studies and urinalysis with protein levels [5].

Table 1: Right heart catheterization: patient's values and normal values

Hemodynamic Parameters	Patient's Values	Normal Values
Right atrium pressure (mmHg)	3	2-6
Right ventricle (s/d)* (mmHg)	80/5	15-30/1-7
Pulmonary artery pressure (s/d/m)* (mmHg)	86/30/50	15-30/8-15/9-18
Pulmonary capillary wedge pressure (mmHg)	3	6-12
Cardiac output (L/min)	2.3	4.0-8.0
Cardiac Index (L/min/m2)	1.6	2.5-4.0
Transpulmonary pressure gradient (mmHg)	47	≤12
Pulmonary vascular resistance (Wood unit)	20.4	<3.125
Cardiac power output (watts)	0.5	<0.6 indicates higher mortality

Heart rate: 107 bpm. Systemic Blood Pressure: 124/83 (97). Body surface area: 1.44 m^2
Pulmonary artery saturation: 55 % Systemic arterial saturation: 97 % (O2 15 l/min via non-rebreather mask) Hemoglobin 13.9 g/dL.
*s/d/m: systolic/diastolic/mean

Case Presentation

A 64-year-old woman with metastatic ovarian cancer presented to the emergency department with progressive shortness of breath on excretion and a dry cough for 3 months, worsening over the past 1 month. The shortness of breath was initially with exertion, now occurring at rest, unrelated to position. She has had an intermittent non-productive cough of the same duration, occurring throughout the day.
Her metastatic ovarian cancer was treated with 6 months of carboplatin, pacilitaxel, and bevacizumab. 3 weeks prior to admission, she was transitioned to paclitaxel and bevacizumab only.

On admission, her oxygen saturation on room air was 85%. Laboratory findings were significant for elevated proBNP 5019 pg/ml and troponin 0.164 ng/ml. A transthoracic echocardiogram revealed a severely dilated right ventricle and atrium with a right ventricular systolic pressure of 77 mmHg. A right heart catheterization (RHC) was performed and showed mean pulmonary artery pressure of 50 mmHg and pulmonary vascular resistance was calculated to be 20.4 Wood units (<3 is normal). (Table 1)

She was admitted to the ICU for treatment of severe PAH with IV and inhaled epoprostenol and sildenafil. She developed severe hypoxia requiring mechanical intubation and eventually required extracorporeal membrane oxygenation (ECMO).
Her course was further complicated by pulseless electrical activity (PEA) arrest and infarcts seen on CT scan of the brain. Given the severity of her condition, the family opted for hospice.

Discussion

Pulmonary hypertension can be classified into five groups based on the World Health Organization [6]. Group 1 is primary pulmonary arterial hypertension (PAH) and is typically idiopathic. This group can be associated with connective tissue diseases and drugs, including amphetamines and chemotherapeutic agents. Though dasatinib and interferons have been linked to PAH, there have been few cases of bevacizumab-induced PAH. There are currently no guidelines for radiographic screening. Furthermore, it is unclear whether screening with echocardiogram or RHC would be beneficial. There are no treatment modalities that have been successful in improving mortality in these patients [7]. ECMO was performed and it also remains unclear if it is useful. Ultimately, more data is required for screening and treatment guidance in bevacizumab-associated PAH.

References

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