Erythrocytosis caused by Vandetanib treatment in metastatic medullary thyroid carcinoma: the first case report

EP67

Mariana Costache Outas, MD, PhD[1], Andrei Colita, MD, PhD[2,3]

[1]Coltea Clinical Hospital, Endocrinology [2]"Carol Davila" University of Medicine and Pharmacy, [3]Coltea Clinical Hospital, Hematology, Bucharest, Romania

INTRODUCTION

Vandetanib is selectively inhibits the tyrosine kinase activity of vascular endothelial growth factor receptor 2 (VEGFR2), thereby inhibiting VEGF-stimulated endothelial cell proliferation and migration and reducing tumour vessel permeability. This agent also blocks the tyrosine kinase activity of epidermal growth factor receptor (EGFR), a receptor tyrosine kinase that mediates tumour cell proliferation and migration and angiogenesis.
Vandetanib has approval for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. Most common side effects to Vandetanib are hypertension, diarrhoea, dermatitis acneiform, prolonged QT and hypothyroidism.

CASE PRESENTATION. INTERVENTIONS. OUTCOMES

We report a 21-year-old man with metastatic medullary thyroid carcinoma (MTC) at diagnosis. The tomography of the chest and abdomen revealed multiple nodular lesions suggestive of metastasis. It was performed a total thyroidectomy with central and cervical compartment dissection, and the patient started thyroid substitution treatment. We followed the patient for the progression of tumour markers of medullary carcinoma (calcitonin level and carcinoembryonic antigen) as well as the metastatic lesions. After an eight months period of follow up, Vandetanib at a dose of 300 mg/day treatment was started due to the progression of the disease, defined as at least a 20% increase in total measured tumour burden (TMTB).
Side effects during a three month period of treatment were hypothyroidism, with increasingly thyroid hormone requirements, diarrhoea and dermatitis acneiform. We observed progressively elevated hematocrit after a week of therapy with a maximum in 4 weeks from the beginning of treatment. Table 1 shows the parameters during treatment.
Hematologic evaluation excluded a primary myeloproliferative neoplasm due to a negative result when tested for the most frequent mutation responsible for Polycythemia Vera located on exon 12 of the Janus kinase 2 (JAK2) tyrosine kinase gene (JAK2 V617F). Serum erythropoietin (EPO) level was within normal range. Four sessions of phlebotomy (300 mL each time) were performed over the following three months, and we add antiaggregant therapy.

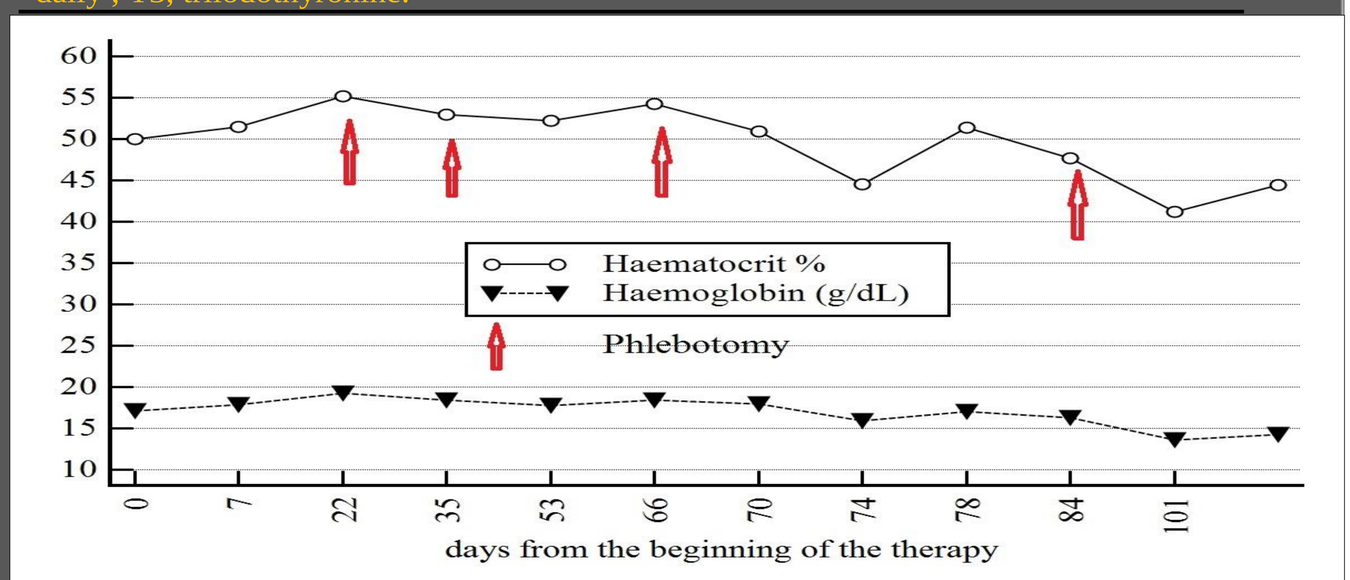
The blood pressure and QTc interval were normal.
Graph 1. shows the hematocrit and haemoglobin levels before and after performing each phlebotomy.

During a three month therapy with Vandetanib, the calcitonin level decreased with 72% with stationary dimensions of the metastasis.

Table 1. The parameters at the Vandetanib initiation and before each phlebotomy

Parameter (units, normal range) / *Date*	*26.02*	*20.03*	*02.04*	*03.05*	*15.05*
	start				stop
Weight (kilograms)	55	56	56	54	55
EPO (UI/L, 4.3-29)		8.5			
Calcitonin (pg/mL, <14.3)	18626	7569		6746	5288
CEA (ng/mL, <3)	545.6				
Haemoglobin (g/dL, 14-17)	17.1	19.3	18.4	18.4	17.02
Haematocrit (%	50	55.2	53	54.3	51.4
RedBloodCell (/µl)	5750	6510	6230	6280	5630
TSH	1.72	9.75	18.9	1.73	0.897
substitution T4 / T3 (weekly dose, µg)	1100/-	1100/-	1250/-	1200/80	1200/80
JAK2 V617F mutation (PCR)	negative				
RET mutations - negative	peripheral blood with analysis of exons 5,7,8,10,11,13,14,16				
RET mutations - tumor tissue	positive codon 918 in exon 16				

EPO= erytropoietin; CEA, carcinoembryonic antigen;T4, Levothyroxine administered daily ; T3, triiodothyronine.



Graph 1. The time of phlebotomy , haemoglobin and hematocrit levels during treatment with Vandetanib

DISSCUSION

Vascular endothelial growth factor (VEGF) is proved to drive angiogenesis and serve as a survival factor for endothelial cells and promotes the abnormal phenotype of blood vessels in tumours but not in the normal adult vasculature.
Studies in animal models proved that drugs that inhibit VEGF signalling by blocking VEGF receptor function induced significant capillary regression that was dose-dependent and varied from organ to organ, with a maximum of 68% in the thyroid. This regression is reversible and most of the capillaries grew back within 2 weeks from the treatment withdrawal.
Erythrocytosis after treatment with anti- VEGF drugs (Sunitinib or Sorafenib) was reported during renal cell carcinoma (RCC) with a concomitant paraneoplastic production of erythropoietin. The erythrocytosis was transient, required a single therapeutic phlebotomy and was related to a sustained major response to the treatment. Erythrocytosis secondary to anti -VEGF treatment was observed in few non-RCC case reports with normal or elevated levels of EPO. No one case with erythrocytosis secondary to Vandetanib was reported.

CONCLUSION

We reported the first case of Vandetanib secondarily induced erythrocytosis in an asymptomatic patient with RET mutation in tumour tissue that has normal levels of EPO and required repeated phlebotomy.

REFERENCES:

1. Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, Ryan AJ, Fontanini G, Fusco A, Santoro M: ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. Cancer Res 2002; 62: 7284–7290.

2. Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth PF, Bigley AL, Hennequin LF: ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 2002; 62: 4645–4655.

3. Inai T, Mancuso M, Hashizume H, Baffert F, Haskell A, Baluk P, Hu-Lowe DD, Shalinsky DR, Thurston G, Yancopoulos GD, McDonald DM (2004) Inhibition of vascular endothelial growth factor (VEGF) signaling in cancer causes loss of endothelial fenestrations, regression of tumor vessels, and appearance of basement membrane ghosts. Am J Pathol 165: 35 – 52

4. Kamba T, Tam BY, Hashizume H, Haskell A, Sennino B, Mancuso MR, Norberg SM, O'Brien SM, Davis RB, Gowen LC, Anderson KD, Thurston G, Joho S, Springer ML, Kuo CJ, McDonald DM (2006) VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol 290: H560 – H576

5. Mancuso MR, Davis R, Norberg SM, O'Brien S, Sennino B, Nakahara T, Yao VJ, Inai T, Brooks P, Freimark B, Shalinsky DR, Hu-Lowe DD, McDonald DM (2006) Rapid vascular regrowth in tumors after reversal of VEGF inhibition. J Clin Invest 116: 2610 – 2621

E-mail: costache.mariana@gmail.com

*This poster was presented at SfE BES **2018**, Glasgow, UK*

BES2018 67--EP

Neoplasia, cancer and late effects

Mariana Cristina Costache Outas

Poster presented at: SfE BES 2018 19–21 November GLASGOW

PosterSessionOnline.com