Int J Clin Exp Med 2016;9(3):6980-6982
www.ijcem.com /ISSN:1940-5901/IJCEM0019092

Case Report

Sunitinib-induced erythrocytosis: case report and review of literature

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Received November 3, 2015; Accepted February 10, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Tyrosine kinase inhibitors (TKIs) are targeted molecular therapies widely used for different types of cancer. Their toxicity profile involves multiple organ systems, and the most common hematological toxicity is myelosuppression. Erythrocytosis is an uncommonly reported side effect of TKIs. We report here a case of erythrocytosis in response to the TKI Sunitinib in a patient with metastatic renal cell carcinoma that resolved with the discontinuation of the medication. The patient remained disease free with normal hemoglobin after three years of follow up. While the mechanism of this side effect remains anecdotal, our case reflects some of the different suggested mechanisms to explain it, including both erythropoietin (EPO) dependent and independent pathways. Further research aimed to reveal these pathways could lead to a general better understanding of the mechanisms governing red cell production and also can be used to gauge and monitor response to treatment with TKIs.

Keywords: Sunitnib, polycythemia, erythropoietin, vascular endothelial growth factor receptor

Case presentation

This fifty two-year-old man, with no significant past medical history, presented to the emergency department with two episodes of hematuria and flank pain occurring one day prior to presentation. He had no dysuria, fever nor systemic symptoms. His vital signs on presentation showed a Temperature of ninety eight degrees Fahrenheit (F), heart rate of 58 beats per minute, respiratory rate of 20 breaths per minute and blood pressure (BP) of 145/69 mmHg. Oxygen saturation was 94% on room air. A CT scan of the abdomen showed the presence of a large renal mass with extension to the renal cortex; urology was consulted, and subsequent nephrectomy confirmed a stage T1bNxMx clear cell renal cell carcinoma. Three years later, a surveillance CT scan of chest showed an 11 mm right middle lobe lung nodule, and wedge resection of the nodule confirmed metastatic renal cell carcinoma. The patient was referred to medical oncology and started on Sunitinib 50 mg daily for four weeks followed by two weeks-off periods each cycle. Patient's BP before initiation of Sunitnib was 134/77 mmHg and his hemoglobin (Hg) was 13.5 gram/dl (g/dl) with hematocrit (Hct) of 36 g/dl. The patient's hemoglobin was noted to rise progressively, and after four cycles, it reached a peak of 19 g/dl, his BP at that time was 159/106 mmHg. Erythropoietin level was elevated to 31.3 mIU/ml; CT scan of abdomen, pelvis and head was negative for malignancy and Jak-2 mutation was negative. One session of phlebotomy was done after which the hemoglobin decreased to 14.2 g/dl, and Sunitinib was resumed, however, the hemoglobin increased again to 17.3 g/dl after two cycles. Decision was made to stop Sunitnib and continue with watchful waiting. Four weeks after medication discontinuation his hg level normalized back to 14.4 g/dl, and BP was also back to 124/84 (**Table 1**). Three years follow up CT scans of abdomen; pelvis and chest remained negative for disease with normal hemoglobin and blood pressure.

Discussion

Targeted molecular therapies are currently the focus of much of the anticancer drug development. Tyrosine Kinase Inhibitors (TKIs) are tar-

Table 1. Timeline of hemoglobin and blood pressure changes with treatment

Before start of treatment	13.5	134/77
After 4 cycles of therapy	19	159/106
After one phlebotomy	14.2	N/A
After 4 weeks of treatment discontinuation	14.4	124/84

geted molecular therapies used in varieties of cancer types, including metastatic melanoma, hepatocellular carcinoma and renal cell carcinoma. Reported side effects of TKIs include asthenia, cutaneous, thyroid, cardiovascular and hematological side effects. Among hematological side effects, anemia is the most common. It developed in 26% of patients treated with Sunitinib as a second-line agent for metastatic clear cell renal cell carcinoma (RCC; 20% grade 2, 4% grade 3, and 2% grade 4) [1]. Similar results were reported in an expanded open access study of Sorafenib as first or second line treatment for RCC [2]. The molecular basis of this side effect [3] is thought to be through TKI-related inhibition of c-kit and other receptors expressed by hematopoietic stem cells leading to myelosuppression. Alexandrescu et al. [4] were the first to report the occurrence of erythrocytosis rather than anemia in response to TKIs. The mechanism of this association is not fully understood. In our case, the patient never smoked, had normal oxygen saturation and Jak-2 mutation was negative. However, the EPO level was increased, suggesting EPO to be the driver of this erythrocytosis. Vascular endothelial growth factor (VEGF) is thought to be a strong negative regulator of erythropoiesis through inhibition of hepatic EPO synthesis, and therefore, high-grade inhibition of vascular endothelial growth factor receptor-2 (VEGFR-2) signaling route by TKIs induces EPO synthesis and drive erythropoiesis [5]. However, more complex molecular interactions are likely to be involved. VEGFR-2 plays another important role in the regulation of vascular tone, and its inhibition results in decreased level of the potent vasodilator Nitric Oxide (NO) and as a result leads to vasoconstriction. This mechanism is thought to account for the TKIs-induced hypertension [6] as observed in our patient and by the same manner it is thought to cause a transient loss of circulating plasma volume and a relative increase in hemoglobin and hematocrit [7]. The differences between those EPO dependent and independent mechanisms are related to the degree of VEGF-receptors. Low potency broad-spectrum VEGF inhibitors as Sunitinib are more likely to act by EPO-independent mechanisms than the higher potency more specific TKI Axitinib [8]. In patients with metastatic renal cell carcinoma, Sunitinib-associated hypertension has been regarded as an efficacy biomarker and thus considered a "positive event" associated with improved clinical outcomes [9, 10]. It can be postulated that the occurrence of Sunitninb-induced erythrocytosis, which share some of the same molecular mechanisms, can be used as an efficacy marker as well, however, further research is needed to validate this hypothesis.

Conclusion

Our case reflects the heterogeneous and not fully understood mechanisms of erythrocytosis in response to TKIs. The wide-spread use of molecularly targeted therapies such as TKIs will pause challenges in recognition and management of their arising side effects. On the other hand, similarly to the occurrence of hypertension, the occurrence of erythrocytosis can be potentially used as a marker of treatment efficacy and hence predicts a better prognosis.

Disclosure of conflict of interest

None.

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