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Case Report

The Abating Effect of Vitamin-C on Imatinib in a CML Patient: A First Case Report

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Abstract

Vitamin C (Ascorbic Acid) is one of the most frequent supplements used for its known antioxidative properties. However, it also has pro-oxidative potential and the potential to interact with certain chemotherapy agents, including Imatinib. Few research papers have investigated the interaction of ascorbic acid and Imatinib, which has been reported to cause imatinib-resistant leukemic cells in mouse models. We present the first case report illustrating the potential blunting effect of vitamin C on imatinib in a with CML interrogated by BCR-ABL rearrangement quantitative PCR. An English-language web search for "CML, Imatinib and vitamin-C interaction /resistance /prooxidative effect" case report revealed no cases reported in the past.

Keywords: CML; Vitamin-C; Imatinib; Reduced; Efficacy; Resistance

Background

Chronic Myeloid Leukemia (CML) is a slow-growing myeloproliferative disorder where the bone marrow produces too many white blood cells. It follows usually a triphasic course starting with a chronic phase, which can develop into an accelerated phase and as the condition, progresses it leads to a blast phase in which immature white blood cells called myeloblasts accumulate in the blood and the bone marrow. The overgrowth of myeloblasts impairs the development of other blood cell lines leading to common symptoms such as fatigue, fever and weight loss [1]. At the molecular level, CML is characterized by the presence of translocation t (9; 22) (q34; q11) which generates the Philadelphia chromosome and the associated fusion gene BCR-ABL1 [2]. This gene leads resistance to genetic instability and resistance apoptosis, hence more cellular proliferation [2]. With the introduction of the tyrosine kinase inhibitor, Imatinib mesylate, which is a BCR-ABL tyrosine kinase inhibitor, treatment outcomes for patients with CML-chronic phase have improved markedly, and hematopoietic stem-cell transplantation is no longer routinely offered as first-line therapy [3,4]. The IRIS trial showed a 5-year Overall Survival (OS) of 96% from the beginning of Imatinib treatment which increased from a 40% OS in the pre-imatinib period in the 1980s [5]. Vitamin C (Ascorbic Acid) is a common dietary supplement. About 40% of Americans take vitamin C supplements and about 1/5 of supplement users take more than 1000mg a day. Adequate nutrition usually provides the necessary dose the body needs. Adult male and female respectively need about 90mg and 75mg of ascorbic acid daily, which can be acquired from a balanced diet. Excessive ascorbic acid intake can affect the absorption of other nutrients. Many studies have investigated Vitamin-C antioxidative effect on scavenging free radicals and reducing the risk of cancer; however, few studies have investigated the pro-oxidative effect of vitamin C and its neutralizing activity toward Imatinib leading to an increase of BCR-ABL transcription [6]. All prior studies on the interaction between vitamin C and Imatinib have been in mouse tumor models and no interaction in humans has been reported in the literature. This case report is the first report illustrating the potential pro-oxidative effect of ascorbic acid on CML cells in the setting of Imatinib treatment.

Case Presentation

A 57-year-old female with a past medical history of hypertension, hyperlipidemia, anxiety disorder, and CML diagnosed in 2014 presented for her regular follow up visits to the oncologist office. Her only complaint was fatigue. In 2014, she was treated with Imatinib. In July of 2017, the patient was in remission for the CML and was taken off Imatinib. In 2018, The Geno-TRACE RT-PCR was performed and revealed a BCR-ABL level of 0.0211%. The patient was put back on Imatinib and since then her BCR-ABL quantitative RT-PCR has been undetectable. During the previous office visit on 5/2020, the patient was found to have a quantitative BCR-ABL translocation of 0.005%, which increased to 0.0258% during the visit in July of 2020. Patient reports compliance to her medications and the only change in her medication list was the addition of Vitron-C and vitamin D_3 2000 units daily for their pro-oxidative effect.

Home medication:

- Hydrochlorothiazide 25mg tablets 1 tablet once daily
- Imatinib 400mg 1 tablet once daily
- Lorazepam 0.5mg 1 tablet once daily
- Losartan 100mg 1 tablet once daily
- Melatonin 3mg 1 tablet once daily as needed
- Multi vitamin tablets Vitamin B 250 mcg 1 tablet once daily
- Vitamin D_3 1000unit 1 tablet once daily
- Vitamin C 1000mg daily OTC (started on 2/2020)
- Vitron C 65mg iron 125mg 2 tablet once daily (started on 2/2020)

Physical exam: Unremarkable

Labs: WBC 6.21. Hemoglobin 11.6. Hematocrit 35.5. Platelet

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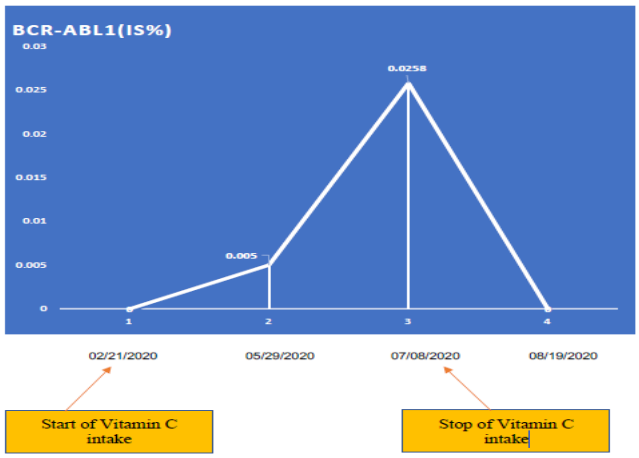

Figure 1: BCR-ABL1 Transcript Level in International Scale (IS %) over Time.

241. BCR-ABL translocation 0.0258%. CMP and the rest of labs unremarkable.

Treatment plan and outcome: On 07/2020, a mutational analysis was ordered to assess whether the patient has some form of underlying mutation causing resistance to imatinib. Also, the patient was asked to stop taking Vitron-C and vitamin C, continue with Gleevec and follow up for the mutational analysis results and BCL-ABL levels in 1 month. On 8/19/2020, BCR-ABL1 level was not detected and ABL1 kinase domain mutations were not detected (Figure 1).

Discussion

This case illustrates the importance of recognizing the pro-oxidative side of ascorbic acid especially for a patient taking certain types of chemotherapy. CML is provoked by the BCR-ABL translocation, which leads to clonal myeloid cell expansion. The tyrosine kinase BCR-ABL activates many intracellular signaling cascades conferring clear advantages for cancer cells. Gleevec is the first-line treatment for CML. It works by inducing *mitochondria*-dependent apoptosis of cancer cells. Vitamin C intake creates a cytotoxic environment for the antineoplastic agents by causing mitochondrial membrane depolarization [7]. When mitochondria are damaged, cells undergo apoptosis, which is the mechanisms of action of several types of chemotherapy, including Imatinib. Vitamin C helps to preserve the health of mitochondria; hence, a negative effect is created against these chemotherapy drugs' mechanism of action [8]. Several research studies have explored the mechanism of how vitamin C acts of the mitochondria and they found that its action mainly dependent on the availability of iron. Through an oxidation-reduction reaction, the iron is reduced by ascorbate to Fe^{2+}, which interacts with oxygen and creates a reactive oxygen species, H_2O_2 which subsequently lead to the formation of a highly reactive hydroxyl radical [6]. In additional to Imatinib, vitamin C has been found to interact with Adriamycin, oncovin and methotrexate with the effect ranging from 30 to 70% reduction in effectiveness of these drugs [8]. For this patient, intake of Vitron-C in addition to over the counter vitamin C supplements correlated with an increase in the levels of BCR-ABL from 0 to 0.005% to 0.025% and a decline to an undetectable level a month later after cessation of intake (Figure 1). Vitron-C, a combination of ascorbic acid and iron, is hypothesized to have led to an oxidation-reduction reaction, creating a ROS species. Furthermore, Vitamin C may have function to preserve mitochondrial function, and impair apoptosis of myeloblast cells leading to an increase of the ABL-BCR level [9]. By protecting the mitochondria, vitamin C may attenuate the efficacy of imatinib.

Summary

This case shows the importance of recognizing the effect of vitamin C with certain anti-neoplastic chemotherapy drugs. This finding could have important clinical relevance given the wide use of vitamin C as a nutritional supplement.

References

1. Zhou H, Xu R. Leukemia stem cells: the root of chronic myeloid leukemia. Protein Cell. 2015; 6: 403-412.
2. Quintas-Cardama A, Cortes J. Molecular biology of bcr-abl1-positive chronicmyeloid leukemia. Blood. 2009; 113: 1619-1630.
3. Santos FP, Kantarjian H, Quintas-Cardama A, Cortes J. Evolution of therapies for chronic myelogenous leukemia. Cancer J. 2011; 17: 465-476.
4. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med. 2017; 376: 917-927.
5. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006; 355: 2408-2417.
6. Kazmierczak-Baranska J, Boguszewska K, Adamus-Grabicka A, Karwowski BT. Two Faces of Vitamin C-Antioxidative and Pro-Oxidative Agent. Nutrients. 2020; 12: 1501.
7. Kluza J, Jendoubi M, Ballot C, Dammak A, Jonneaux A, Idziorek T, et al. Exploiting mitochondrial dysfunction for effective elimination of imatinib-resistant leukemic cells. PLoS One. 2011; 6: e21924.
8. Heaney ML, Gardner JR, Karasavvas N, Golde DW, Scheinberg DA, Smith EA, et al. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. Cancer Res. 2008; 68: 8031-8038.
9. Walz C, Sattler M. Novel targeted therapies to overcome imatinib mesylate resistance in Chronic Myeloid Leukemia (CML). Crit Rev Oncol Hematol. 2006; 57: 145-164.