CLINICAL VIGNETTE

A Potential Case of Blood Orange Induced Imatinib Toxicity

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I have strong memories of visiting my grandmother in Florida, coming to the breakfast table every morning to see my grandmother start her day, with a grapefruit sliced in half accompanied by the Wall Street Journal. Later in life as she was no longer able to live independently, I would be called upon to review her medications, and identified multiple medications that could have been affected by her daily breakfast ritual. Although we may forget grapefruits interaction with medication clearance, most physicians are familiar with it. We report a case of possible toxicities from an alternate citrus, I never felt the need to inquire.

The patient is a 39-year-old woman who presented to the hospital with a multi-month history of shortness of breath and leukocytosis after failing multiple courses of antibiotics. Hematologic evaluation led to the diagnosis of chronic myelogenous leukemia in chronic phase, confirmed by BCR/ABL FISH on bone marrow biopsy. Peripheral blood counts included WBC as high as 54k and platelets as high as 748 in setting of mild anemia. She had a newborn at home, who fortunately was no longer breast feeding, was recently married, with an understandably overwhelmed husband. He felt helpless and wanted to encourage supplements, and already ordered Arbon wellness shakes, and was stressing dramatic nutritional changes. He, like many, expressed understandable anxiety and his instinct was to do everything they could imagine out of fear, despite their initial impulse they listened to my rational description of therapies and reassurance and the importance of imatinib and that any additional supplements could unknowingly affect this lifesaving medication. She started on imatinib at 400 mg, and quickly achieved a hematologic remission and a complete molecular remission was imminent after just a couple months of therapy. They celebrated, she was tolerating the medicine with minimal side effects and some normalcy had returned. A few months later she developed fatigue and routine lab work revealed new anemia, with platelets decreased to as low as 41, with mild neutropenia. We reviewed the timing of her medication but it was relatively acute, and labs less than a month before were essentially normal. I asked about supplements, wellness cocktails and dietary changes, and remembered the initial friction regarding supplements and assumed this was the culprit. There were no new medications, I remembered my grandmother and asked about grapefruit. The patient was very proactive and had in a short time educated herself about CML and imatinib and was well aware grapefruits were potential problem. After a brief interruption in imatinib her counts returned to normal. At her follow up visit we were anticipating re-challenge with imatinib when she confirmed what she already knew about grapefruits, but asked if blood oranges could have similar effects with medications and admitted in a somewhat embarrassed tone that when this all happened she had bought a large quantity from a local bulk retail chain and had consumed nearly the whole volume herself in a matter of days. I admitted that I had seen blood oranges in a cooking show, but had never seen one myself and knew very little about them, including medical interaction.

Blood oranges originate in the Mediterranean dating as far back as the 18th century, with three main strains, the Tarocco from Italy, Sanguinelo from Spain and Moro from Sicily.[1] They differ from other orange varieties in that they produce a red pigment known as anthocyanin, leading to the deep red colored flesh that they are known for and individual harvest and species variability.[2] PubMed search reveals no evidence that this pigment has any medication interactions, however it can interact with CYP3A4 with 3-D modeling.[3] Whereas there is minimal medical literature about blood oranges specifically or linking anthocyanin pigments on medication and CYP interactions, the processes of grapefruits are very well described. Grapefruits contain furanocouramins which interact with CYP3A4 irreversibly.[4] Imatinib is primarily metabolized by cytochrome P450 3A4 (CYP3A4).[5] Additionally several other citrus species, most notably Seville oranges have been linked to CYP3A4 inhibition.[6]

I cannot say with any level of certainty what strain/species of blood orange my patient ingested. In fairness, I cannot even say with absolute conviction that the citrus ingested was in fact a blood orange as marketed. By the time the patient and I had made the connection the fruit was no longer available. The timing was highly suspicious for the citrus causing a temporary impact on imatinib clearance. Fortunately, the patient continues to do well, has reached a major molecular response and is close to a complete molecular response. She continues to tolerate imatinib with no further cytopenias. We present this case as a reminder that interactions between diet and medications can be complex, particularly in the expansive biodiversity in agriculture and global economies.

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