

# <u>Clinical Pharmacology & Toxicology Pearl of the Week</u> ~ Adverse Reactions to Alternative Therapies in Medical Oncology ~

# Case:

- A 60-year-old male with advanced colorectal cancer undergoing chemotherapy with oxaliplatin and capecitabine presents with severe fatigue, nausea, and generalized weakness. On initial investigations, he was found to have an acute kidney injury, with Creatinine 728 µmol/L. He was found to be oliguric, producing ~300 ml/day of urine.
- On further history, in addition to his chemotherapy agents and antinauseants, the patient has been taking **high-dose intravenous vitamin C** (IVC) at 50 grams per day.

#### **Background:**

- Complementary and alternative medicine (CAM) use among cancer patients is common, with herbal products being the most frequently used.
- CAMs can interact with antineoplastic agents, leading to diminished metabolism of therapy agents (thereby leading to toxicity) or potentially reducing treatment efficacy.
- High-dose vitamin C is often used by cancer patients as an adjunct to chemotherapy, driven by its purported benefits in enhancing chemosensitivity and reducing side effects. However, the safety and efficacy of this practice remain controversial.
- High-dose IVC can lead to significant adverse effects, including oxalate nephropathy, hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, and potential interactions with chemotherapeutic agents that may reduce their efficacy.

# **Clinical Features:**

- Acute kidney injury may present with symptoms of uremia (fatigue, nausea, generalized weakness), elevated serum creatinine, and oliguria.
- <sup>-</sup> Laboratory tests revealed hyperoxaluria and elevated serum oxalate levels, consistent with high-dose vitamin C administration. Therefore, the most likely etiology of his AKI was oxalate nephropathy.

#### Management:

- Immediate discontinuation of high-dose IVC was essential. The patient was hydrated aggressively with intravenous fluids to promote renal excretion of oxalate.
- Hemodialysis was considered due to the severity of renal impairment. Nephrology was consulted, however the patient improved with supportive management, and did not require renal replacement therapy.

# **Case Resolution:**

- Over a period of approximately 2 weeks, the patient's serum creatinine levels normalized, and urine output increased.
- The patient was counseled on the risks of using high-dose vitamin C and advised to avoid such therapies in the future.
- The chemotherapy regimen was resumed with close monitoring for any further adverse reactions.

# Examples of Other Adverse Reactions with Alternative Therapies in Medical Oncology:

- **Cannabinoid Drug-Drug Interactions:** Medications commonly used in oncology (warfarin, buprenorphine, tacrolimus) may lead to pharmacokinetic drug-drug interactions with cannabis and/or cannabinoids.
  - These interactions are mediated by the inhibition of cytochrome P450 enzymes (CYP3A4, CYP2C9, and others) by cannabinoids, which can alter the metabolism of these drugs.
- **Neutropenia**: Interactions between natural compounds, including diosmin (citric fruits), escin (horse chestnut seeds), and resveratrol (grapes, berries, peanuts, and red wine) with ribociclib (CDK4/6 inhibitor, used in advanced hormone receptor positive breast cancer) can lead to profound neutropenia, with reported cases of febrile neutropenia.
- **Cardiotoxicity**: Hawthorn (Crataegus spp., rose shrub) may exacerbate the cardiotoxicity of anthracyclines, increasing risk of heart failure and arrhythmias.
- **Apricot Pits and Cyanide Toxicity**: Amygdalin, found in apricot kernels, has been studied for its potential anticancer properties, and is commonly used as a CAM for prevention and treatment of prostate cancer. However, there is minimal evidence supporting its efficacy. Further, the risk of cyanide poisoning is significant.
  - High doses of amygdalin can lead to cyanide toxicity, presenting with symptoms such as cardiovascular collapse and metabolic acidosis. Therefore, the risk-benefit balance of using amygdalin for cancer treatment is negative.
  - A level of 20 µg/kg body weight of cyanide in blood is cited in the literature as a toxicity threshold in humans, which can be obtained with just 1-2 pits in a 70kg adult. In case studies, adults were found to have cyanide toxicity with 20 or more pits, whereas just three pits in children.

# Summary:

- This case highlights the risks of unregulated CAM therapies during chemotherapy.
- It is crucial to take a thorough medication history that includes CAMs, when considering drug toxicity, adverse reactions, or decreased efficacy.

# **References:**

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- 7. EFSA Panel on Contaminants in the Food Chain (CONTAM). Acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels. Efsa Journal. 2016 Apr;14(4):e04424.

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