HEMATOLOGY, TRANSFUSION AND CELL THERAPY

www.htct.com.br

POSTER PRESENTATIONS

ADULT HEMATOLOGY
ACUTE LEUKEMIAS

PP 01

Hypercalcemia due to the interaction between all trans retinoic acid and posaconazole used for acute promyelocytic leukemia treatment

H. Afacan Öztürk, M. Albayrak, S. Maral*, M. Reis Aras, F. YıLmaz, P. Akyol, M. Tiglioglu

University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Hematology, Ankara, Turkey

Objective: All-trans retinoic acid (ATRA), a physiological metabolite of vitamin A, has revolutionized acute promyelocytic leukemia (APL) treatment. Most APL cases show a t(15;17) (q22 q21) chromosomal translocation from which a PML/retinoic acid receptor a (RARa) fusion gene originates. The maturation of APL cells during myeloid differentiation is blocked at the promyelocyte stage, and ATRA induces the terminal differentiation and apoptosis of leukemia cells. Although very high rates of complete remission have been achieved using ATRA in APL patients, side effects associated with systemic ATRA treatment have also been reported in the literature. Hypercalcemia associated with ATRA has been reported among rare side effects of the drug. We report a case of hypercalcemia that resulted from the interaction of ATRA and posaconazole used in the treatment APL.

Case report: A 49-year-old woman was diagnosed with APL by tests and studies to investigate the etiology of pancytopenia, and was started on a combination of daunorubicin 60 mg/m^2/day (3 days), cytosine arabinoside 100 mg/m^2/day (7 days) plus ATRA 45 mg/m^2/day. Due to febrile neutropenia, piperacillin/tazobactam treatment and posaconazole treatment at a dose of 300 mg/day were added. She developed difficulty breathing and weight gain on the 6th day of therapy, which was attributed to the ATRA syndrome; thus, ATRA was stopped and dexamethasone was started. As she developed hyperbilirubinemia during her follow-up, posaconazole and prophylactic drugs were stopped. The patient entered remission after induction therapy, and ATRA plus idarubicin 5 mg/m^2/day (4 days) chemotherapy regimen, and prophylactic posaconazole were planned as the first consolidation therapy. Having a normal calcium level (9.79 mg/dL; normal range 8.6–10.2 mg/dL) prior to treatment, the patient developed a progressive rise of serum calcium (10.3 to 10.6 to 10.8 to 11.1 mg/dL) with the start of posaconazole and ATRA. Her Vitamin D level and PTH, both of which were in the normal range. Considering that hypercalcemia might have been caused by posaconazole and ATRA, both drugs were stopped. When the calcium level returned to normal by four days, ATRA but not posaconazole was reinstituted, and the patient developed no calcium elevation thereafter.

Conclusion: It is known that ATRA is metabolized by Cytochrome P450 pathway, and closely associated with the enzymes CYP 2C9 and CYP3A4. Azole antifungals have been shown to be strong inhibitors of the cytochrome P450 enzyme system. A case of hypercalcemia developing as a result of the addition of voriconazole to ATRA was reported in the literature, and another case of hypercalcemia developing as a result of combined use of itraconazole and ATRA. To reduce the incidence of side effects during ATRA treatment, it may be prudent to limit the use of any drug with the potential of inhibiting the cytochrome P450 enzyme system. A review of the literature has not provided any clear evidence as to when ATRA can be reinstituted after the cessation of a drug belonging to the azole group. This case highlights the importance of monitoring ATRA's side effects when it is used in combination with drugs inhibiting the cytochrome P450 enzymes.

https://doi.org/10.1016/j.htct.2020.09.063