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Case Study

Acalabrutinib Induced Headache

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ABSTRACT

A 72-year-old female was diagnosed with Waldernstorm's macroglobulinemia in January 2017, and the patient was started on rituximab, bortezomib, and dexamethasone for three cycles. Response assessment after three cycles revealed progressive disease. After this, the patient defaulted and took native treatment. In January 2023, the patient presented with gum bleeding and fatigue. The complete blood count was deranged. Taking her age into concern, she was started on the targeted therapy Bruton's tyrosine kinase inhibitor (BTK) capsule acalabrutinib 100 mg two times a day. After taking the capsule acalabrutinib, she experienced a throbbing headache, which was relieved by the intermittent stoppage of therapy and indomethacin.

INTRODUCTION

On November 21, 2019, the Food and Drug Administration approved acalabrutinib for chronic lymphocytic leukemia. The initial approved dose was 100 mg two times a day [1] Acalabrutinib is a second-generation Bruton's tyrosine kinase inhibitor (BTK). BTK is an important enzyme in B-cell antigen receptor pathway (BCR). By inhibiting BTK, acalabrutinib inhibits the proliferation of B- B-cells. BTK has prominent roles in the activation pathways involved in the survival of B- lymphocytes such as Akt and NF-κb and secretion of chemokines such as CCL3 and CCL4. Since many such downstream molecules are involved, inhibition of BTK can result in apoptosis of lymphocytes. More specifically acalabrutinib binds covalently to cysteine 481 moiety on the BTK and prevents its autophosphorylation.[2] Acalabrutunib was mainly developed with the intent of avoiding the off-target effects of ibrutinib with similar therapeutic outcomes.[3,4] Overall acalabrutininb was well tolerated and most of the adverse effects were grade 1 or grade 2 in phase 2 clinical trials. The most common ones reported ones are headache, diarrhoea and upper respiratory infection. Grade 3 adverse effects included hypertension, neutropenia and pneumonia.[5,6,7]

CASE REPORT

A 72-year-old woman was diagnosed with chronic lymphocytic leukemia (Waldernstorm's macroglobulinemia) in January 2017, Following

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which she was started on rituximab , bortezomib, and dexamethasone for 3 cycles. After treatment patient had progressive disease. Later, the patient did not follow up with the hospital and took other treatment modalities. The patient returned in January 2023 with gum bleeding and fatigue, her hemoglobin was found to be 4.5 g/dl, and her platelet count was 1,50,000 cells/dl. Later the patient was started on the tablet acalabrutinib 100 mg twice daily. After this, the patient experienced a throbbing headache, which was gradual in onset, started three to four hours after taking the medication, typically being fronto-temporal accompanied by nausea and vomiting. Relieving factors were lying down in a closed dark room without lights. Aggravating factors were exposure to light. When the patient stopped taking the acalabrutinib capsule, she did not experience headaches. Patient took tablet paracetamol 500 mg which did not provide any symptomatic relief. Later patient took a capsule of indomethacin 25 mg, after which she experienced symptomatic relief. The patient continued to take a capsule of indomethacin along with an acalabrutinib capsule. But later, in view of advice given by the treating doctor, she took paracetamol for headache. In 20 days, the headache settled, and the patient did not take paracetamol anymore. Currently, the patient experiences only occasional headaches with a frequency of one to two times every month. Now, her hemoglobin is 9.5 g/dl.

DISCUSSION

Headache is usually seen with the second-generation BTK inhibitor acalabrutinib. Clinical trials data demonstrate that nearly seventy percent of patients, especially in the first cycle, experience headaches.[6,8] Headache settles with time. The headache is reported to respond to treatment with non-steroidal anti-inflammatory drugs, paracetamol, and caffeine. Dose modification or interruption of treatment can probably reduce the intensity of the headache.

CONCLUSIONS

More research is required to find if dose modification or treatment interruption has a role in reducing throbbing headaches due to second-generation Bruton's tyrosine kinase inhibitors. Slowly as more evidence continues to emerge add-on therapy to tyrokine kinase inhibitors can reduce their duration of therapy and also their adverse events. Since Bruton's tyrosine kinase inhibitors can remain a mainstay of treatment for chronic lymphocytic leukemia, it is of utmost importance that caregivers recognize such adverse events and get them managed appropriately.

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