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Case Report

Synchronous Pneumonitis, Hepatitis and Enteritis Under Treatment with PI3kδ Inhibitor Idelalisib for Follicular Lymphoma

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Abstract

Idelalisib is approved for the treatment of relapsed follicular lymphoma. We report a case with multiple toxicities during treatment including pneumonitis, hepatitis and enteritis. Toxicities resolved under supportive treatment. Idelalisib was discontinued. Our patient achieved partial remission of follicular lymphoma and had no further late complications.

Keywords: Enteritis; Follicular Lymphoma Case Report; Hepatitis, Idelalisib; Pneumonitis

Introduction

Idelalisib, a phosphatidylinositol 3-kinase (PI3K) δ inhibitor, is approved for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma or relapsed chronic lymphocytic leukemia in combination with rituximab, as well as small lymphocytic lymphoma for patients with two or more previous systemic treatments.

PI3K, in its activated form, regulates through phosphorilation of membrane lipids, intracellular enzymes responsible for cell proliferation, survival and migration. The δ isotope of PI3K is expressed on lymphocytes and is responsible for transimitting signals from the B-cell receptor and other chemokine receptors to its intracellular target AKT. AKT in its turn activates signaling pathways that promote cell proliferation such as the Mammalian Target Of Rapamycin (mTOR) complex.

Based on the above findings, studies on PI3Kδ blockade, through its inhibitor idelalisib, have shown promising results. Patients with relapsed follicular lymphoma after treatment with rituximab and alkylating agents received idelalisib 150mg bid. The overall respose rate was 57%, median duration of response was 11 months, while overall survival was 20.3 months [1]. The median duration of treatment was 6.6 months.

Common adverse events included diarrhoea or enteritis, fatigue, nausea, cough and pyrexia. The most common grade 3 adverse event was pneumonia, whereas the most common laboratory abnormality was elevation of transaminases serum alanine (ALT) and aspartate aminotransferase (AST).

Case Report

We report a case of a 62-year old male patient with relapsed follicular lymphoma. Initial diagnosis of follicular lymphoma, grade I (WHO classification), was 8 years ago in stage IIIA (Ann Arbor staging). He received R-CHOP chemotherapy achieving partial remission, followed by consolidation radiation of the paraaortal lymph nodes. Three years later he presented a left paravetrebral relapse and received a second-line therapy with rituximab and bendamustine, followed by a 2-year rituximab maintenance. Histological findings reported follicular lymphoma grade II. Again, he received consolidation radiation of the paravertrebral infiltrate. Two years after completing rituximab maintenance he had a relapse at the left submandibular lymph node region and nasopharynx. Histology was repeated, confirming low grade follicular lymphoma grade II without transformation. Idelalisib was initiated as third-line therapy.

After four weeks of treatment the patient experienced mild diarrhoea. The laboratory results showed relevant elevation of transaminases (ALT and AST). Medication with idelalisib was not discontinued, four weeks later transminases raised further (Figure 1). An MRI for lymphoma staging was performed showing partial response, while laboratory results showed partial resolution of transaminase elevation. The patient complained about headaches and muscle cramps.

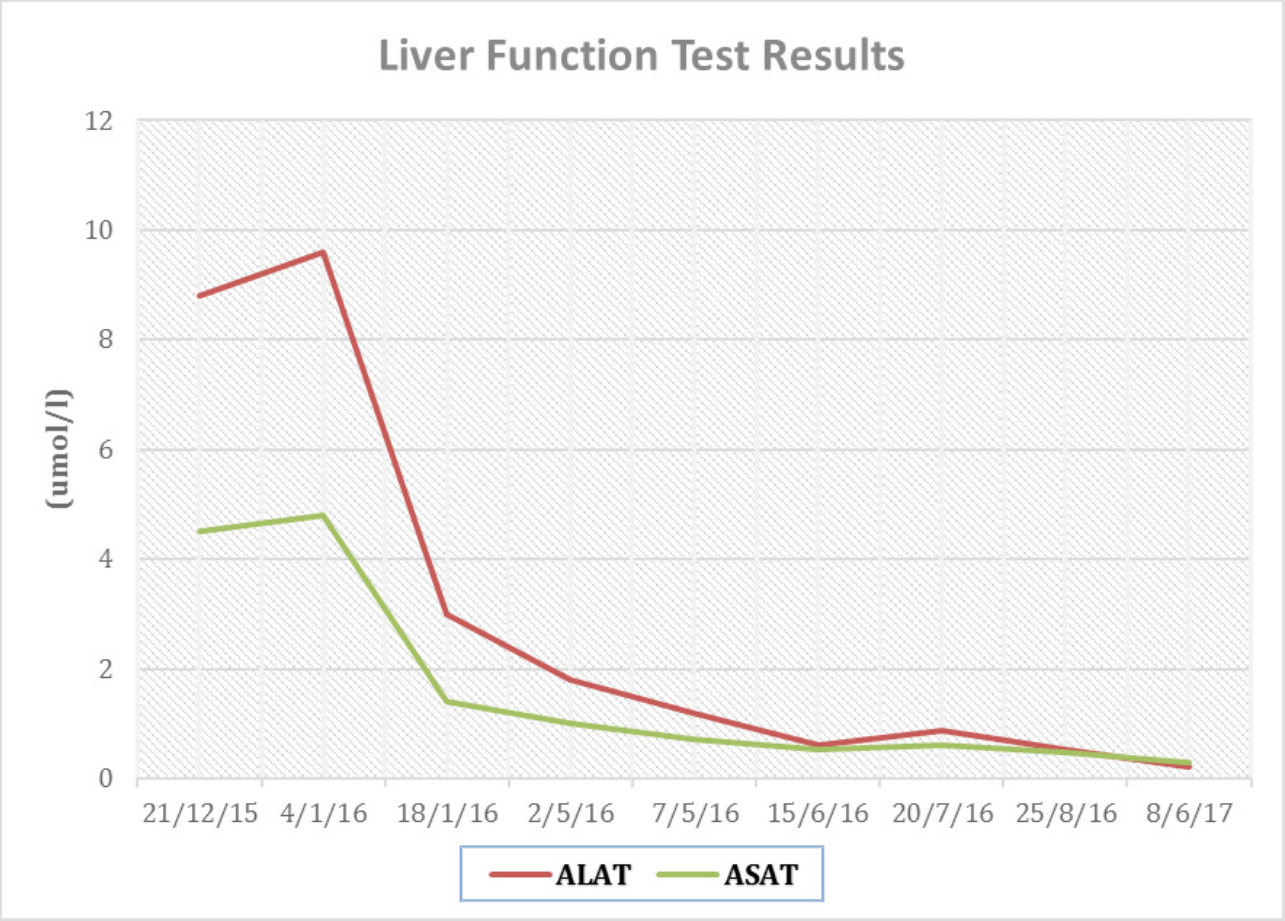

Figure 1: Elevation of transaminases (ALAT: serum alanine, ASAT: aspartate aminotransferase). Normal range 0,17-0,85 μmol/l.

During the fourth month of treatment the patient reported intermittent fever and coughing. Saturation was not restricted. Chest CT-scan revealed signs of pnemonitis (Figure 2) such as interstitial infiltrates. As respiratory symptoms slowly resolved, diarrhoea and fever developed, accompanied by skin rash. The patient was admitted in the hospital and administered supportive care consisting of intravenous fluids and topical steroids for the skin rash. His symptoms resolved completely. Idelalisib was discontinued after an overall period of 6 months on treatment. Radiological findings showed a significant benefit with partial response of follicular lymphoma.

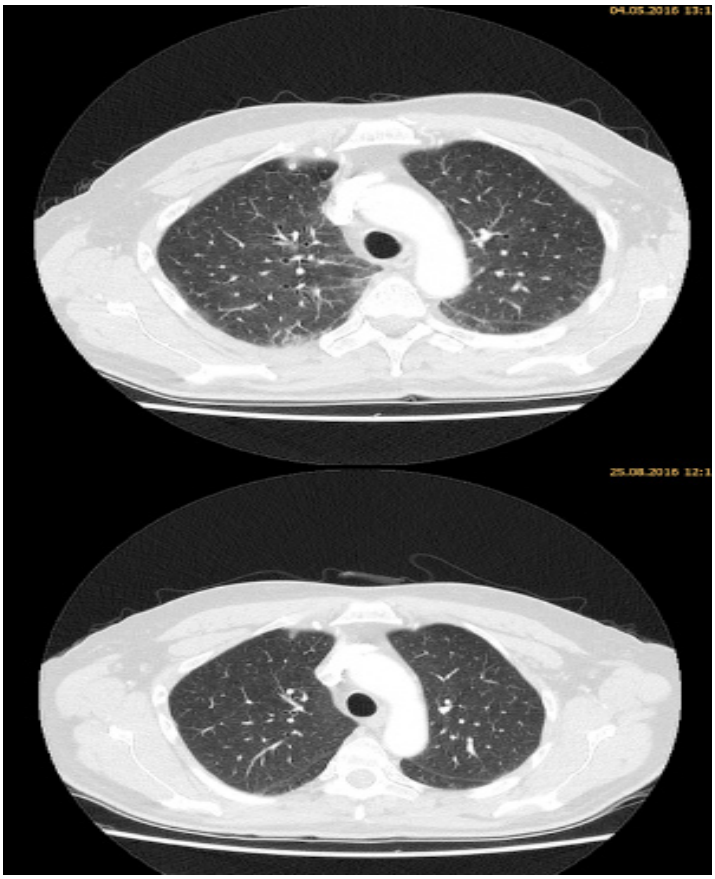

Figure 2: Chest CT showing interstitial infiltrates and bilateral basal ground-glass opacities (upper image) and their resolution after a 3-month period (lower image).

Discussion

Treatment with idelalisib has set a new standard for patients with relapsed follicular lymphoma. The mechanism of action is selective for lymphocytes and highly effective. Nevertheless, frequent side effects include pneumonitis, asymptomatic elevation of transaminases often referred as hepatitis, as well as enteritis. The exact pathogenetic mechanism of these side effects has not yet been fully explained.

The development of pneumonitis should be suspected when patients report coughing or dyspnoea, when hypoxia or desaturation is measured or when interstitial infiltrates appear in chest-CT scan. The appropriate treatment consists of steroids [2].

Hepatotoxicity or hepatitis characterized by elevation of transaminases, often asymptomatic, is commonly referred as transaminitis. Elevations of ALT and AST can reach up to >5x the Upper Limit of Normal (ULN). The majority of patients temporary interrupted idelalisib, but were able to resume treatment. It is recommended to monitor ALT and AST every 2 weeks for the first 3 months, then every 4 weeks for the next 3 months and afterwards once every 1-3 months. Elevation 3-5 of ULN should be monitored but idelalisib can be continued, between 5 and 20 of ULN treatment should be interrupted and resumed at lower dose, whereas greater than 20 ULN treatment should be permanently interrupted [3].

Gastrointestinal toxicity in form of diarrhoea or enteritis presented in the literature at a median time of 1.9 months. Although grade 1/2 diarrhoea seem to appear earlier (1,5 months) and respond good to loperamide, grade 3/4 usually develop later (7,1 months) and should be treated with budenoside and steroids. On both cases presence of infectious agents or other causes of diarrhoea should be excluded in advance [3].

Duration of treatment for our patient was similar to published data. Our patient achieved partial remission, which was held up to date, 2 years after treatment initiation.

Although the above toxicities as well as their appropriate treatment have been well described, this is the first case where all 3 common toxicities occurred synchronously. As treatment with idelalisib becomes popular, monitoring for toxicities and specific treatment should be prompt.

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Author Contributions

Conceived and designed the experiments: MV. Analysed the data: MV, DJ. Wrote the first draft of the manuscript: MV. Contributed to the writing of the manuscript: MV, DJ, NG. Agree with manuscript results and conclusions: MV, DJ, NG. Jointly developed the structure and arguments for the paper: MV, DJ, NG. Made critical revisions and approved final version: MV, NG. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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