Alectinib-induced anemia with acanthocytosis: To proceed or discontinue treatment in Non-Small Cell Lung Cancer patients?

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ABSTRACT

ALK gene rearrangements are important oncogenic driver alterations in non-small-cell lung cancer and a predictive factor. When present, it enables the use of tyrosine kinase inhibitors, such as Alectinib. This drug can lead to anemia and erythrocyte morphological changes. We present the case of a 72-year-old patient diagnosed with stage IV non-small cell lung cancer treated with Alectinib in the first line. The drug was very effective in reducing the tumor size but with G2 anemia and acanthocytosis as side effects. Anemia was improved once Alectinib was replaced by Brigatinib.

Keywords: Adverse events; tyrosine kinase inhibitors; non-small-cell lung cancer; treatment

INTRODUCTION

Anaplastic Lymphoma Kinase (ALK) gene encodes the enzyme ALK, a tyrosine kinase responsible for the activation of multiple pathways associated with cell proliferation and differentiation[1]. ALK gene rearrangements are oncogenic molecular driver alterations, present in about 5% of patients with non-small-cell lung cancer (NSCLC).[2]

Alectinib is a highly selective tyrosine kinase inhibitor (TKI) of the ALK protein, which is constitutively activated via this gene translocation.[2] The higher systemic and brain efficacy of Alectinib (second-generation TKI) compared to Crizotinib (first-generation ALK inhibitor) is associated with significant survival benefits. [3] Therefore, Alectinib and other next-generation ALK inhibitors are the current standard treatment for newly diagnosed advanced ALK+ NSCLC.

Nevertheless, Alectinib is associated with hematological toxicities, namely anemia, reticulocytosis, and abnormal erythrocyte morphology, such as the prevalence of acanthocytes.[2]

CASE REPORT

We present the case of a 72-year-old woman, a non-smoker, with a personal history of hypertension and hypercholesterolemia, properly treated and controlled with pharmacological therapy.

In December 2019, she was diagnosed with an adenocarcinoma of the left lung, stage IV-B (cT2b N3 M1b), with a PD-L1 of 70%. The molecular analysis of the tumor revealed the presence of an alteration in the *ALK* gene, which was the EML4::ALK rearrangement.

In January 2020, she initiated treatment with Alectinib 600 mg twice a day. The first imaging evaluation with computed tomography (CT) scan, in March 2020, demonstrated stable disease with tumor dimensions of 48x41 mm. The next CT scan in July 2020 revealed a partial response, with a tumor dimensional reduction to 32x23 mm.

In September 2020, nine months after the initiation of treatment, the patient presented G2 normocytic anemia with a hemoglobin of 9.1 g/dL (baseline hemoglobin level was 12.4 g/dL). Lactate dehydrogenase (LDH) was slightly higher than the normal upper limit, but no other abnormal laboratory parameters were found. Since the patient was asymptomatic, she proceeded with the treatment.

In November 2020, a new CT scan revealed a tumor dimensional reduction to 10x9 mm. However, two months later, in January 2021, the patient presented a hemoglobin level of 8.4 g/dL, and the anemia became microcytic (mean globular volume of 79 fL), with a high red cell distribution width (RDW). Iron levels were normal but close to the normal lower limit. Every other parameter related to anemia was within normal range, including transferrin, ferritin, bilirubin, LDH, vitamin B12 and folic acid levels. Renal, liver, and thyroid function tests were also normal. The patient had no complaints and denied any visible blood loss. She continued Alectinib at the same dose and an iron supplementation was initiated with a small improvement in the evaluation of March 2021 (Hb 9.3 g/dL).

The patient continued the treatment until October 2021, with stable disease, but new hemoglobin decreased to 8.6 g/dL with a mean globular volume of 82 fL. Further blood analysis revealed reticulocytosis, high ferritin, and slightly high LDH. The levels of iron, folic acid, B12 vitamin, transferrin, haptoglobin, and erythropoietin were normal, and so were the renal, liver, and thyroid function tests. Thalassemia was excluded through hemoglobin electrophoresis, and gastrointestinal endoscopic studies were normal. The patient remained asymptomatic and continued taking oral iron supplementation and Alectinib 600 mg twice daily, despite G2 microcytic anemia (hemoglobin between 8.5 and 9.4 g/dL). The following CT scans, performed in 2022 continued to show stable disease in the lung.

In February 2023, the patient was referred to a Hematology appointment, due to sustained anemia. Further studies were performed, namely a blood smear and a bone marrow evaluation. Examination of the peripheral blood smear revealed abnormal morphology of the erythrocytes, compatible with acanthocytes. The bone marrow smear and biopsy were normal.

Consequently, in March 2023, Alectinib was discontinued and switched to Brigatinib, an alternative tyrosine kinase inhibitor. In May 2023, two months later, the anemia was only G1 with a hemoglobin of 10.6 g/dL, normocytic, and no other abnormal values were found.

DISCUSSION

In this case report, the patient was diagnosed with NSCLC/ALK+ and Alectinib was used as first-line targeted therapy for 38 months, with a favorable clinical response, but with low-grade anemia after eight months of treatment as the main adverse effect.

According to the ALEX study, the percentage of patients with Alectinib-induced anemia (any grade) is about 20%, and grade 3 or 4 anemia is less than 5%.[3] This anemia can be associated with erythrocyte morphological changes, like acanthocytosis. Acanthocytes refer to contracted erythrocytes exhibiting multiple membrane projections, in contrast with the recognizable discoid structure of the normal red cell.[1] There are some cases of Alectinib-induced erythrocyte membrane changes already described in the literature, however, the mechanism remains unknown. Besides acanthocytes, other red cell membrane changes such as spherocytes, echinocytes, and dacrocytes are linked to Alectinib.[2 4]

It remains unclear whether this is a dose-dependent effect, and published data reports anemia with acanthocytosis as a specific side effect unique to Alectinib, rather than a TKI-associated effect.[1] Moreover, anemia seems to be reversible, as it is evident in the reported clinical case with recovered from G2 to G1 anemia in our patient, when Alectinib was switched to Brigatinib.

Continuing Alectinib with routine blood film examinations and regular haemolytic markers may be reasonable for asymptomatic patients with only morphological changes on blood smear examination.[1] On the other hand, when anemia appears in blood analyses, the interruption of treatment depends on the characterization of anemia. If one is facing hemolytic anemia (G2 or superior), Alectinib must be temporarily withheld until resolution, then resumed at a reduced dose (from 600 mg twice a day to 450 mg twice a day).[5] The discontinuation of the treatment in these situations will be more determined by the patient's symptoms rather than the hemoglobin value alone. In our patient, G2 anemia was well tolerated. This compelled us to proceed with Alectinib for more than three years. However, since prolonged anemia is also a cardiovascular risk factor, the decision to discontinue Alectinib was taken after a multidisciplinary meeting.

CONCLUSION

Alectinib induces anemia (hemolytic and non-hemolytic) and red blood morphology changes. Precaution must be taken when using this medication in patients with known anemia or hemoglobinopathies. In these situations, an alternative ALK inhibitor should be considered. Blood film examinations and regular haemolytic markers should be undertaken in patients receiving Alectinib, to allow early detection of hematological toxicity and therapeutic adjustments.

The diagnosis and management of toxicities of new targeted agents in Oncology benefits from a multidisciplinary approach and inter-physician communication.

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