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Alectinib-Induced Immune Hemolytic Anemia in a Patient with Lung Adenocarcinoma: Case Report and Literature Review

Chai Young Lee, Yon Ju Ryu*

Division of Pulmonary and Critical Care Medicine, College of Medicine, Ewha Womans University, Seoul, Republic of Korea
Email: *medyon@ewha.ac.kr

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Abstract

Alectinib is a selective Anaplastic Lymphoma Kinase (ALK) tyrosine kinase inhibitor used as standard therapy for ALK-rearranged lung adenocarcinoma. Hemolytic anemia is considered a rare but significant adverse event of alectinib. Here, we report the case of a 78-year-old female with advanced ALK rearrangement-positive lung adenocarcinoma who developed grade 4 drug-induced hemolytic anemia after receiving alectinib as first-line therapy. We discontinued alectinib treatment and switched to brigatinib. As a result, anemia improved without recurrence of lung adenocarcinoma over one year.

Keywords

Non-Small Cell Lung Cancer, Alectinib, Brigatinib, Hemolytic Anemia, Drug-Induced Hemolytic Anemia

1. Introduction

Anemia is a commonly encountered problem in cancer patients receiving chemotherapy, with or without radiation [1] [2]. However, Drug-Induced Hemolytic Anemia (DIHA) is relatively rare, with an estimated incidence of approximately one case per 1 - 2 million individuals [3]-[5]. DIHA is usually mild, but is occasionally associated with acute severe hemolytic anemia and death [4]. Therefore, the possibility of DIHA should always be considered when using the offending drugs. Recently, several drugs against various molecular targets have been developed, resulting in a remarkable improvement in the prognosis of lung cancer. Alectinib is a selective anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor used as standard therapy for non-small cell lung cancer harboring an ALK fusion gene [6] [7]. Anemia due to alectinib has been reported to account for 6%

- 26.3% of adverse events [8]. To the best of our knowledge, alectinib-induced hemolytic anemia has never been described in the literature in Korea, but there are potentially many other similar cases that have not been reported.

Here, we report a case of a 78-year-old female with ALK-positive adenocarcinoma of the lung who developed grade 4 anemia due to alectinib-induced hemolytic anemia.

2. Case Presentation

A 78-year-old Asian female, a non-smoker, presented with chest Computed Tomography (CT) abnormalities and no symptoms at our hospital in August 2019. The chest CT revealed a 2.8 cm tumor in the right lower lobe of the lung and diffusely scattered nodules in the right pleura and fissural area (**Figure 1**). After a comprehensive examination, the patient was diagnosed with lung adenocarcinoma, specifically clinical T1cN2M1a stage IVA with ALK-rearrangement positivity. Accordingly, alectinib (600 mg) was administered orally twice daily as first-line treatment in September 2019, which induced a partial response and was subsequently continued.

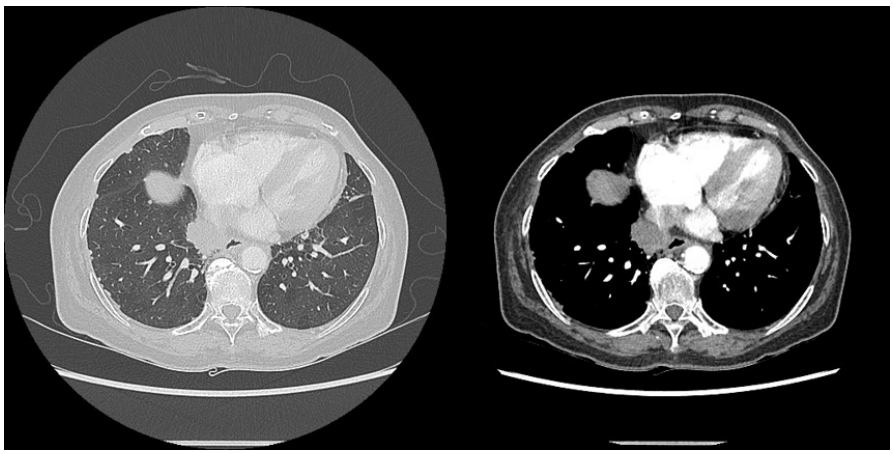

Figure 1. Chest computed tomography prior to the initiation of alectinib showed a 2.8 cm size tumor in the right lower lobe of the lung and diffusely scattered nodules in the right pleura and fissural area.

However, laboratory findings showed progressive anemia. The initial hemoglobin level was 11.6 g/dL before starting alectinib therapy. Two months after the initiation of alectinib, the hemoglobin level had decreased to 8.2 g/dL. The patient was referred to the hematology department in July 2020 and diagnosed with macrocytic, hyperchromic anemia related to chronic disease combined with anemia from chemotherapy. About three years after starting treatment, the hemoglobin level gradually decreased to 6.7 g/dL. The patient was referred to the hematology department again in April 2022. Laboratory findings showed elevated levels of total bilirubin (1.83 mg/dL), low levels of reticulocytes (5.01%), and haptoglobin (< 8 mg/dL) (**Table 1**). Folic acid and vitamin B12 levels were normal. Spherocytes appeared on a peripheral blood smear (**Figure 2**), and the

results of the Direct Antiglobulin Test (DAT) were negative. There was no evidence of active bleeding as determined by upper and lower gastrointestinal endoscopy. We also confirmed no recurrence of lung cancer and no splenomegaly by contrast-enhanced CT.

Table 1. Laboratory data.

Test	Result
Hematology	
WBC	4940/μL
RBC	1.92×10^6/μL
Hb	6.7 g/dL
Hct	20.6%
MCV	107.2 fl
MCH	35.1 pg
MCHC	32.7%
Plt	164×10^3/μL
Ret	5.01%
Urinalysis	
Specific gravity	1.012
Proteinuria	1+
Hematuria	(-)
Glucosuria	(-)
Biochemistry	
T-Bil	1.83 mg/dL
D-Bil	0.37 mg/dL
AST	33 U/L
ALT	24 U/L
ALP	77 U/L
BUN	46 mg/dL
Cr	1.35 mg/dL
Na	136 mEq/L
K	5.1 mEq/L
Cl	108 mEq/L
TP	6.9 g/dL
Alb	4.0 g/dL
Fe	157 μg/dL
UIBC	226 μg/dL
Ferritin	516 ng/mL
Folic acid	> 37 ng/mL
Vit B12	1211 pg/mL
Haptoglobin	< 8 mg/dL

Continued

Serology	
CRP	0.06 mg/dL

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Plt: platelets, Ret: reticulocyte, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: asparatate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, Cl: chlorine, TP: total protein, Alb: albumin, Fe: serum iron, UIBC: unsaturated iron binding capacity, CRP: C-reactive protein.

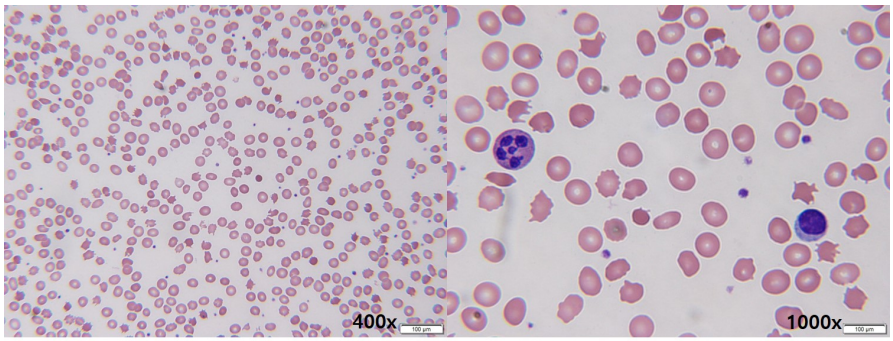

Figure 2. Spherocytes were observed on peripheral blood smears.

Based on the clinical course during the period of alectinib administration, the patient was diagnosed with alectinib-induced hemolytic anemia. We instructed the patient to discontinue alectinib in May 2022. The patient required a blood transfusion once, but there was no further progression of anemia. Two months after discontinuing alectinib, the hemoglobin level increased to 9.8 g/dL. Other laboratory findings also indicated the resolution of hemolytic anemia. The total bilirubin level was 0.61 mg/dL, the reticulocyte count was 1.23%, and the haptoglobin level was 38 mg/dL. The total bilirubin level and hemoglobin level are shown in (**Figure 3**).

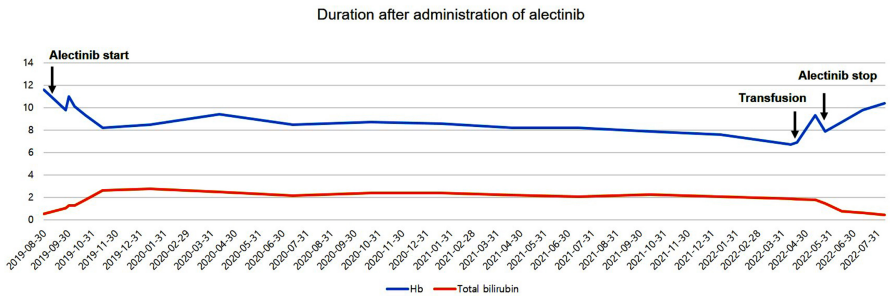

Figure 3. Changes in blood levels of hemoglobin and T-Bil after the administration of alectinib. Hemoglobin levels decreased, whereas the T-Bil levels gradually increased after alectinib administration. T-Bil: total bilirubin.

Treatment was switched to brigatinib in July 2022. The patient has been taking brigatinib for over a year without any evidence of cancer recurrence. The pa-

tient's hemoglobin level has consistently remained above 10.0 g/dL.

3. Discussion

To the best of our knowledge, this is the first reported case of hemolytic anemia caused by alectinib in Korea. In this case, alectinib-induced hemolytic anemia gradually progressed to grade 4 over two years after starting treatment with alectinib, and improved after discontinuation of the drug.

DIHA is typically mediated by immunologic mechanisms and infrequently occurs through non-immunologic mechanisms [5] [9]. Immune-mediated mechanisms are classified into three types: hapten-drug adsorption, immune-complex formation, and the production of true autoantibodies. In hapten-drug adsorption, hemolytic anemia usually occurs due to IgG class antibodies against drug epitopes. This leads to the elimination of red blood cells (RBCs) coated with the drug and anti-drug antibodies in the spleen. On the other hand, immune-complex mechanisms involve either complement-related direct cell destruction following the binding of the drug-RBC antibody complex or the development of autoantibodies. In all immune-mediated cases, antibodies are found, and DAT is usually positive. Non-immunologic mechanisms involve the deposition of proteins on RBCs, which accelerates cytoplasmic clearance [4] [10].

In line with previous studies, the results of the DAT were negative in this case [11]-[14]. The DAT detects the presence of antibodies or complement on the surface of RBCs. The negative DAT result suggests that the hemolysis was occurring via a nonimmune mechanism. Alectinib has been found to induce subclinical hemolysis in some patients, accompanied by morphological changes in erythrocytes, such as acanthocytes or spherocytes [12] [15]. We also observed the presence of spherocytes on a peripheral blood smear, suggesting that alectinib-induced hemolytic anemia is possibly related to RBC oxidative stress. Further investigation is needed to better understand the mechanism underlying Alectinib-related hemolysis.

In a previous study, the median time from the start of alectinib to the first episode of hemolytic anemia was 56 days, with 75% of cases occurring within 90 days of drug exposure [16]. In this case, although DIHA was diagnosed approximately three years after starting alectinib treatment, total bilirubin levels were already elevated above baseline two months after alectinib administration. We did not initially recognize DIHA, because anemia is prevalent in cancer patients, especially those undergoing cancer-directed treatment. Additionally, tests such as peripheral blood smear, haptoglobin, and DAT were not performed at that time. As the anemia progressed, further hematological tests were conducted, and the patient was ultimately diagnosed with DIHA.

In conclusion, we report a case of grade 4 hemolytic anemia induced by alectinib in a patient with ALK-positive lung adenocarcinoma. Most cases of DIHA are reversible upon discontinuation of alectinib. Therefore, regular hematologic monitoring is recommended during alectinib treatment. DIHA should be considered in patients with progressive anemia.

Conflicts of Interest

The authors declare no conflicts of interest associated with this manuscript.

References

[1] Ludwig, H., Müldür, E., Endler, G. and Hübl, W. (2013) Prevalence of Iron Deficiency across Different Tumors and Its Association with Poor Performance Status, Disease Status and Anemia. *Annals of Oncology*, **24**, 1886-1892. https://doi.org/10.1093/annonc/mdt118

[2] Ludwig, H., Van Belle, S., Barrett-Lee, P., Birgegård, G., Bokemeyer, C., Gascón, P., *et al.* (2004) The European Cancer Anaemia Survey (ECAS): A Large, Multinational, Prospective Survey Defining the Prevalence, Incidence, and Treatment of Anaemia in Cancer Patients. *European Journal of Cancer*, **40**, 2293-2306. https://doi.org/10.1016/j.ejca.2004.06.019

[3] Garbe, E., Andersohn, F., Bronder, E., Klimpel, A., Thomae, M., Schrezenmeier, H., *et al.* (2011) Drug Induced Immune Haemolytic Anaemia in the Berlin Case-Control Surveillance Study. *British Journal of Haematology*, **154**, 644-653. https://doi.org/10.1111/j.1365-2141.2011.08784.x

[4] Garratty, G. (2009) Drug-Induced Immune Hemolytic Anemia. *Hematology*, **2009**, 73-79. https://doi.org/10.1182/asheducation-2009.1.73

[5] Greene, E.M. and Hagemann, T.M. (2017) Drug-Induced Hematologic Disorders. In: Dipiro, J.T., Talbert, R.L., Yee, G.C., Matzke, G.R., Wells, B.G., Posey, L.M., Eds., *Pharmacotherapy: A Pathophysiologic Approach*, McGraw-Hill Education, 10e. https://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146079796

[6] Peters, S., Camidge, D.R., Shaw, A.T., Gadgeel, S., Ahn, J.S., Kim, D., *et al.* (2017) Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *New England Journal of Medicine*, **377**, 829-838. https://doi.org/10.1056/nejmoa1704795

[7] Hida, T., Nokihara, H., Kondo, M., Kim, Y.H., Azuma, K., Seto, T., *et al.* (2017) Alectinib versus Crizotinib in Patients with ALK-Positive Non-Small-Cell Lung Cancer (J-ALEX): An Open-Label, Randomised Phase 3 Trial. *The Lancet*, **390**, 29-39. https://doi.org/10.1016/s0140-6736(17)30565-2

[8] Mok, T., Camidge, D.R., Gadgeel, S.M., Rosell, R., Dziadziuszko, R., *et al.* (2020) Updated Overall Survival and Final Progression-Free Survival Data for Patients with Treatment-Naive Advanced ALK-Positive Non-Small-Cell Lung Cancer in the ALEX Study. *Annals of Oncology*, **31**, 1056-1064. https://doi.org/10.1016/j.annonc.2020.04.478

[9] Jäger, U., Barcellini, W., Broome, C.M., Gertz, M.A., Hill, A., Hill, Q.A., *et al.* (2020) Diagnosis and Treatment of Autoimmune Hemolytic Anemia in Adults: Recommendations from the First International Consensus Meeting. *Blood Reviews*, **41**, Article 100648. https://doi.org/10.1016/j.blre.2019.100648

[10] Mayer, B., Bartolmäs, T., Yürek, S. and Salama, A. (2015) Variability of Findings in Drug-Induced Immune Haemolytic Anaemia: Experience over 20 Years in a Single Centre. *Transfusion Medicine and Hemotherapy*, **42**, 333-339. https://doi.org/10.1159/000440673

[11] Okumoto, J., Sakamoto, S., Masuda, T., Yamaguchi, K., Horimasu, Y., Miyamoto, S., *et al.* (2021) Alectinib-Induced Immune Hemolytic Anemia in a Patient with Lung Adenocarcinoma. *Internal Medicine*, **60**, 611-615. https://doi.org/10.2169/internalmedicine.4241-19

[12] Kunz, J., Wiedemann, C., Grosch, H., Kriegsmann, K., Gryzik, S., Felden, J., *et al.* (2022) Early Development of Ubiquitous Acanthocytosis and Extravascular Hemolysis in Lung Cancer Patients Receiving Alectinib. *Cancers*, **14**, Article 2720. https://doi.org/10.3390/cancers14112720

[13] Yuan, Y., Mapp, S. and Xu, W. (2020) Two Cases of Marked Red Cell Anisopoikilocytosis and Haemolysis with Alectinib, an Anaplastic Lymphoma Kinase Inhibitor. *British Journal of Haematology*, **190**, 642-642. https://doi.org/10.1111/bjh.16813

[14] Gullapalli, V., Xu, W., Lewis, C.R., Anazodo, A. and Gerber, G.K. (2021) A Multi-Centre Case Series of Alectinib-Related Erythrocyte Membrane Changes and Associated Haemolysis. *Journal of Hematopathology*, **14**, 131-136. https://doi.org/10.1007/s12308-020-00427-3

[15] Kuzich, J.A., Heynemann, S., Geoghegan, N., Evelyn, C., O'Mahoney, S., Wilson, S., *et al.* (2021) Alectinib Induces Marked Red Cell Spheroacanthocytosis in a Near-Ubiquitous Fashion and Is Associated with Reduced Eosin-5-Maleimide Binding. *Pathology*, **53**, 608-612. https://doi.org/10.1016/j.pathol.2020.10.023

[16] Dores, G.M., Nayernama, A., Cheng, C., Moureaud, C. and Jones, S.C. (2022) Hemolytic Anemia Following Alectinib Reported to the U.S. Food and Drug Administration Adverse Event Reporting System. *American Journal of Hematology*, **97**, e129-e132. https://doi.org/10.1002/ajh.26454

Abbreviations

DIHA: drug-induced hemolytic anemia; ALK: anaplastic lymphoma kinase; CT: computed tomography; DAT: direct antiglobulin test; RBCs: red blood cells.