

Ibrutinib Treatment and EGFR-mutant Lung Adenocarcinoma

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Ibrutinib is a novel active Bruton's tyrosine kinase (BTK) inhibitor approved for the treatment of several types B-cell hematologic malignancies.

Clinical trials in chronic lymphoid leukemia (CLL) patients reported a very promising result with ibrutinib treatment. The RESONATE trial (ClinicalTrials.gov number, NCT01578707) clearly demonstrates superiority for progression-free survival and overall survival in the ibrutinib-treatment group. In addition to the prolongation of overall survival, some cases of secondary solid malignancy development in CLL patients have been described as having a potential negative impact on patient prognosis.

The Surveillance, Epidemiology, and End Results (SEER) Program data on 2028 patients showed increased risk for secondary malignancy in CLL patients over expected risk in general population and did not find a detrimental effect from CLL treatments [1]. In contrast, other publications have described hematologic malignancies, MDS/t-AML tumors, and Richter's transformation, triggered by fludarabine and cyclophosphamide (chemotherapy) drugs plus rituximab (FCR) protocol [2]. Influence of new biological drugs, such as ibrutinib, on secondary non-hematological cancers is still unclear. We present a case of secondary non-small cell lung adenocarcinoma (NSCLCA) in CLL patient developed under ibrutinib treatment.

PATIENT DESCRIPTION

A 77-year-old man with no significant co-morbidities, history of smoking, or family cancer history was admitted to our oncology department with a diagnosis of CLL. Due to disease progression, he initially underwent FCR protocol. Later, the treatment protocol was changed to ibrutinib at a standard dose of 420 mg/day. This treatment set the patient into a durable complete remission. After 10 months of Ibrutinib treatment, a follow-up computed tomography (CT) scan showed a new 4 cm left lung upper lobe lesion associated with malignant pleural effusion. Tissue pathology was compatible with a primary non-small cell lung adenocarcinoma. Molecular analysis showed an epithelial growth factor receptor (EGFR) exon-19 deletion mutation (EGFR-mut NSCLCA).

Erlotinib protocol was initiated to treat EGFR-mut NSCLCA. The dose was gradually increased to the standard 150 mg/day dose as recommended. The previously scheduled ibrutinib protocol was unchanged. The observed adverse events of erlotinib included skin rash, dryness, and acne. Later, the daily dose of erlotinib was reduced due to repeated episodes of skin toxicity. After 4 months, the 18F-fluorodeoxyglucose positron-emission tomography/CT re-evaluation showed decrease in lung tumor size and complete disappearance of pleural effusion.

Ten months later, the patient developed progressive lung metastasis and repeated the EGFR test. This test detected a new EGFR mutation: T790 m. There were no signs of CLL progression. Ac-

ording to this new molecular analysis, the patient's treatment was changed to osimertinib at standard dose without any reported side effects. Under this treatment, in following 4 months the patient demonstrated both EGFR-mut NSCLCA tumor and CLL stable disease. Three months later, the patient started to complain of progressive weakness. Clinical examination revealed multiple palpable lymph nodes. A biopsy showed Richter's transformation of CLL with 70% proliferation index. The patient refused salvage treatment and died.

COMMENT

Currently, in cases of secondary cancer appearance, the trigger of its development remains unclear. During the last decade, a new class of biological drugs has been developed, added to the clinical oncology arsenal, and introduced into standard treatment protocols. Tyrosine-kinase inhibitors (TKIs) are one of the most commonly used group of biological drugs, having multiple biological targets including EGFR, BRAF, MET, RET, and ALK. Both erlotinib and osimertinib, which were prescribed during treatment of our patient, are anti-EGFR agents.

Our case demonstrates the new clinical oncology reality, when a patient treated by a new biological drug for potentially fatal hematologic malignancy develops another deadly tumor. In CLL patients the incidence of secondary solid tumors is extremely rare.

BTK is the molecular target of ibrutinib. The BTK pathway influences intracellular signaling mechanisms of cytokine re-

ceptors, lymphocyte surface antigens, and cell-matrix adhesion receptors. It plays an important role in normal regulation of different immune cells [3]. Considering these multiple signal transduction pathways and possibility of secondary mutations during TKI treatments, ibrutinib cannot be excluded as potential trigger factor for secondary lung cancer development.

In our particular case, after the patient was diagnosed with secondary lung cancer the clinical dilemma of administering a combined biological drug treatment was raised. We did not find any clinical data reporting concomitant treatments of ibrutinib and erlotinib or osimertinib.

To optimize patient treatment, we were challenged to provide answers for the following questions: can pharmacokinetic drug interaction be safely excluded? Are the recommended drug doses safe for simultaneous treatment? What is the risk magnitude of overlapping serious adverse events? Not less important, in the decision-making process, the possible detrimental effects of different TKI combinations should also be considered.

Pharmacokinetic drug interactions may affect the toxicity rate by increasing plasma TKIs concentrations, or alternatively, may cause drug resistance by decreasing TKIs plasma concentration. Ibrutinib and erlotinib have a similar pharmacokinetic profile. Both are primarily metabolized by cytochrome P450 3A4 and are influence activity of P-glycoprotein. Therefore, in our case, the starting dose of erlotinib was initially reduced. In addition, we recommended that our patient avoid drugs and food known as inducers or inhibitors of CYP3A. No

high-grade adverse events of erlotinib or ibrutinib were observed within the full dose schedule. Unfortunately, there was no possibility to examine the drug's blood concentration and to define the therapeutic levels. However, the laboratory and radiological follow-up demonstrated clinical effectiveness of both treatments. This fact led us to assume that both drugs reached the therapeutic concentration.

Our case raises some interesting aspects. Treatments using TKIs have been shown to induce secondary malignancy and molecular alterations and mutations that contribute to the development of treatment resistance. The cell analysis of such iatrogenic malignancies may demonstrate multiple molecular changes including high rate of RAS mutation, activation of MAPK-pathway signaling, and ERK-mediated transcription that are interpreted as TKIs treatment consequences [4]. However, ibrutinib has shown an occasional affinity to different types of kinases including EGFR. During the cell-culture experiment, ibrutinib was found to be a selective inhibitor of EGFR-mutant NSCLCA. In addition, this study showed the appearance of complete resistance to further erlotinib treatment [5]. Therefore, theoretically ibrutinib may have potential effect in prevention of EGFR-mutant cancer. However, our clinical case demonstrated a possible opposite effect because the secondary tumor progressed during ibrutinib treatment with further proven effectiveness of erlotinib and osimertinib, which are both anti-EGFR drugs.

We think our experience will help in the understanding of the consequences of biologic treatments. We assume that ibrutinib

can influence multiple tyrosine-kinase pathways, which may induce a driver mutation for development of second primary tumors.

CONCLUSIONS

In patients with EGFR-mutant NSCLCA developed under ibrutinib treatment, an anti-EGFR TKIs treatment can be effective and safely prescribed. Simultaneous treatment of synchronous malignancies with TKIs combinations is challenging and promising. Additional clinical and research data are needed to explore iatrogenic mutations and their influence on secondary malignancy development.

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Life is made of ever so many partings welded together.

Charles Dickens (1812-1870), English writer and social critic

Vocations which we wanted to pursue, but didn't, bleed, like colors, on the whole of our existence.

Honoré de Balzac (1799-1850), French novelist and playwright