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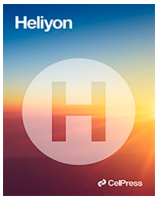

Case report

Chronic myeloid leukemia during osimertinib treatment in a non-small cell lung cancer patient: A case report

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ABSTRACT

Case summary: A 45-year-old man presented with a 4.0cm × 4.0cm mass in right lower lobe and a right lower lobectomy was performed. The pathological diagnosis from the right lower lobe mass was adenocarcinoma with an EGFR mutation in exon 21 (L858R). He chose osimertinib as postoperative adjuvant treatment. Eight months after the administration of osimertinib, leukocytosis was detected and we diagnosed the patient with chronic myeloid leukemia (CML). After the diagnosis was made, the patient started the treatment of flumatinib immediately, and treatment of osimertinib continued. After one month treatment, leukocytosis was completely relived. The patient was receiving treatment of osimertinib and flumatinib simultaneously with both lung cancer and leukemia well-controlled, and the side effects were tolerable.

Conclusion: Hemogram of non-small cell lung cancer (NSCLC) patients should be carefully monitored during EGFR-TKIs treatment. While there is a potential association between EGFR-TKIs and the development of hematologic abnormalities such as CML, more evidence is needed to clarify whether EGFR-TKIs have a leukemogenic effect. For patients with CML during EGFR-TKIs treatment, osimertinib combined with flumatinib may be an effective treatment modalities and the side effects can be tolerated.

1. Introduction

Therapy-related myeloid neoplasm(t-MN) is a rare but fatal complication. According to the current WHO classification, t-MNs are generally categorized into myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and myelodysplastic/myeloproliferative neoplasm (MDS/MPN) based on current WHO definition [1]. Chronic myeloid leukemia(CML) is an uncommon manifestation of t-MN.

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are targeted agents for patients with EGFR-mutant NSCLC. Given that EGFR-TKIs have shown good efficacy in advanced NSCLC patients, it also promotes the use of EGFR-TKIs in postoperative NSCLC patients. The ADAURA study highlighted osimertinib, a third-generation EGFR-TKI, as a treatment with remarkable efficacy, a favorable safety and toxicity profile, and excellent tolerability in the adjuvant therapy of NSCLC patients [2].

This report details a rare case of therapy-related CML manifesting eight months after osimertinib monotherapy in postoperative NSCLC patients. Additionally, we provide a literature review on cases of t-MN that occurred during EGFR-TKIs treatment.

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1.1. Case presentation

A 45-year-old man presented to the hospital with a chest computed tomography(CT) scan showing a 4.0cm × 4.0cm mass in right lower lobe, without any signs of hilar or mediastinal lymph nodes enlargement (Fig. 1A). The patient subsequently underwent a right lower lobectomy and formal ipsilateral mediastinal lymph node dissection (Fig. 1B). Postoperative pathological diagnosed as adenocarcinoma, with the lymph node dissection revealing metastatic involvement of the 7th group mediastinal lymph node. The patient was staged as pT2bN2M0 (IIIa) lung adenocarcinoma. A further gene examination confirmed epidermal growth factor receptor (EGFR) mutation in exon 21(L858R). He refused chemotherapy and in favor of receiving osimertinib as postoperative adjuvant treatment. Oral administration of Osimertinib commenced two months postoperatively, at a dosage of 80mg/day (Fig. 2A).

Eight months after the initiation of osimertinib treatment, a complete blood count revealed elevated levels of white blood cell (28310/μL), absolute neutrophil (18120/μL) and platelet count (733000/μL). Physical examination and abdominal sonography showed no evidence of lymphadenopathy, hepatomegaly or splenomegaly. Bone marrow aspirate smears revealed a granulocytic blast rate of 87.5 %. Eosinophil levels in the bone marrow were increased to 9.5 %. Karyotype analysis of bone marrow showed 46,XY,t(9; 22)(q34.1; q11) [3]. BCR-ABL(210) fusion gene was positive. Based on all the laboratory findings, a final diagnosis of CML was made. Given the patient's concurrent diagnosis of CML, a secondary malignancy following NSCLC, and the uncertain safety of osimertinib combining flumatinib, treatment with flumatinib was initiated at a reduced dose of 400mg/day, 200mg lower than the standard dose recommended in the prescribing information. In the meantime, treatment of osimertinib continued(80mg/d). After one month of treatment, leukocytosis was completely resolved and complete blood count reduced to normal (Fig. 2B). The patient experienced mild adverse effects, including grade 1 diarrhea, grade 1 oral ulcers, and grade 1 abnormal liver function, according to CTCAE criteria. Consequently, we adjusted the dose of flumatinib to 600mg/day. One year after the diagnosis of CML, the patient's clinical condition remained stable, and was still on the follow-up (Figs. 1C and Fig. 2A).

2. Discussion

To the best of knowledge, this is the first case of CML arising following monotherapy with EGFR-TKIs, specifically osimertinib, in the treatment of NSCLC. This case is considered a t-MN rather than primary CML despite the absence of prior cytotoxic chemotherapy or radiotherapy. The patient achieved a sustained complete hematological response (CHR) following treatment with a combination of osimertinib and flumatinib, and NSCLC remained well controlled.

T-MNs are fatal complications that arise from mutations primarily induced by prior chemotherapy and/or radiation therapy of malignancies, solid tumors, and autoimmune disease [1,3,4]. Previous studies suggested risk factors of T-MN including exposure to alkylating agents, topoisomerase (TOP) II inhibitors, radiation therapy [5,6]. More recently, some other drugs such as purine analogues and Poly(ADP-ribose) polymerase (PARP) inhibitors were also associated with the development of t-MN [7].

Normally, patients are at greater risk of developing myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) than CML. In a cohort research, a total of 113 t-MNs with complete clinical data were categorized, and 94.7 %(107/113) were diagnosed with MDS or AML at onset [8]. Such findings may ascribe for that CML arises from primitive stem cells, which are more frequently resting and therefore less affected by DNA damage [9]. Typical chromosome abnormality of CML is characterized by translocation of a limited region of chromosome 22 (the breakpoint cluster region [BCR]) and an oncogene located on chromosome 9 (ABL) [10], which causes BCR-ABL1 fusion protein and activates tyrosine kinase. However, MDS and AML have multiple cytogenetic and molecular disorders [8]. In conclusion, chromosome abnormality additional to Ph chromosome in CML is rare compared to AML [11]. Therefore, it is difficult to differentiate t-MN from de novo CML based on chromosome disorder, because both can share same genetic features (especially Ph chromosome).

EGFR-TKIs show remarkable antitumor activity in patients with EGFR mutation, and have become standard first-line treatment for such patients with advanced NSCLC and in their postoperative adjuvant therapy. According to the data collected from FDA adverse event reporting system (FAERS), only 2.7 % of adverse effects were associated with blood and lymphatic system disorders [12]. Ten patients who developed t-MN after receiving EGFR-TKIs treatment had been reported in the literature [13–17]. Among them, five patients received Gefitinib, five patients received Erlotinib. As for the type of induced leukemia, most of them were AML and MDS, only one case was CML after EGFR-TKIs treatment. Moreover, all patients had a clinical history of antecedent cytotoxic therapy or

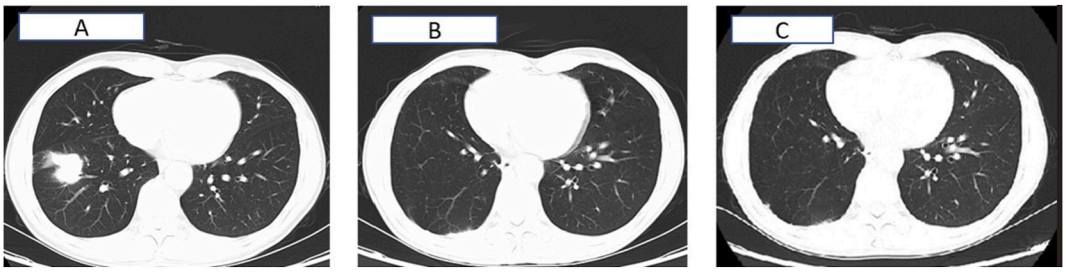

Fig. 1. CT scan of the lung. (A) before surgery; (B) 2 month after surgery; (C) performed in April 2023, indicating the lung cancer was well-controlled.

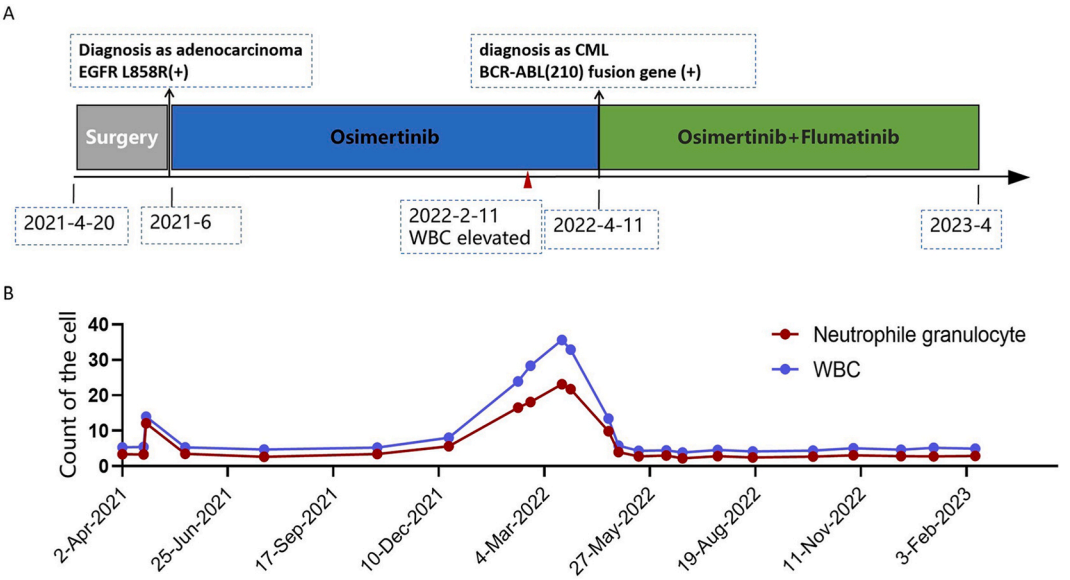

Fig. 2. Timeline summarizing the different therapeutic sequences and count of blood cells. (A)After the diagnosis of CML, treatment of flumatinib started at a dose of 400mg/day, and gradually increased to 600mg/d. (B) After one month treatment of flumatinib, leukocytosis was completely relived and complete blood count reduced to normal.

radiotherapy before EGFR-TKIs treatment. Despite only a few patients reported hematopoietic abnormality, the risk of EGFR-TKIs causing leukemia should not be ignored. Previous article has proposed EGFR-TKIs may induce the BCR-ABL fusion gene [18]. Unfortunately, such idea has never been proven.

In our case, while the patient may have developed a therapy-related malignancy, the possibility of de novo CML still exists. It is difficult to differentiate t-MN from de novo CML based on chromosome disorder, because both can share same genetic features (especially Ph chromosome) [15]. However, it is worth noting that this patient chose osimertinib for postoperative adjuvant therapy without any antecedent cytotoxic therapy or radiotherapy. Furthermore, the patient had no previous exposure to any known bone marrow toxic materials. During the first eight months treatment of osimertinib, the patient's peripheral counts remained normal. Therefore, attributing the development of CML solely to a pre-hematologic disorder or earlier myelotoxic exposure appears insufficient. Up to now, there have been no reports on the secondary therapy-related malignancy after osimertinib itself. And it is unclear by what mechanism osimertinib may be acting to promote CML.

With respect to latency period, the risk of patients with previously existed solid tumor being diagnosed with t-MN increased within 9–12 months after treatment, peaked at 2 years, and gradually reduced to baseline within 10–15 years [19]. Although most of t-MN tend to develop 1–10 years after the initiation of treatment, the interval between EGFR-TKI treatment and leukemia is comparatively shorter (5.5 month–26 months) [17,20]. In present case, the interval was 8 months, which is relatively short (See in Table 1).

Over the past years, BCR-ABL1 tyrosine kinase inhibitors (TKIs) as the first-line treatment for CML have dramatically increased the survival and quality of life for CML patients. The life expectancy of patients with CML is now approaching that of the general population [21]. According to previous clinical experience of imatinib, patients are expected to achieve CHR, defined as the resolution of disease symptoms and normalization of hematologic parameters within 3 months [22]. A Phase 3, randomized, open-label, multi--center study showed flumatinib had higher rates of responses, deeper and faster response than imatinib [23]. In the present case, the patient reached CHR within 1 month after the administration of flumatinib, showing an optimal response. Notably, osimertinib therapy was continued concurrently with flumatinib administration. In our case, after one month of flumatinib treatment, the patient reached CHR, but the following treatment decision was still an exploratory process. Three treatment plans were proposed. The first option was to continue treatment of flumatinib while withholding further treatment for lung cancer. Considering the patient was diagnosed with IIIA stage NSCLC, the risk of recurrence remained high. A double-blind, phase three trial showed in II/IIIA stage NSCLC patients, about 45.8 %(157/343) of patients observed recurrence without any adjuvant therapy after operation, while only 10.9 % (37/339) of EGFR-positive patients observed recurrence after the administration of osimertinib [24]. The second choice was continuing treatment of flumatinib combining adjuvant chemotherapy. Very few articles mentioned the combining use of TKIs and adjuvant chemotherapy. Choukri Elm'hadi et al. reported a case of synchronous CML and metastatic relapse of breast cancer, and the patient received a successful treatment of imatinib and docetaxel simultaneously without hematologic toxicity [25]. The last choice was administrating flumatinib and osimertinib together, aiming at CML and NSCLC respectively. However, the safety of using two molecularly targeted agents at the same time remains unknown. The patient selected the last treatment plan in the end. We started the treatment of flumatinib at lower dose in concern of toxicity. Moreover, we strengthened the monitoring of adverse event during the treatment, and fortunately, only mild diarrhea (CTCAE 1 grade) and rash (CTCAE 1 grade) were noticed.

Considering the risk of developing t-MN and bone marrow inhibition, hemogram of NSCLC patients should be carefully monitored

Table 1
patients who developed t-MNs after EGFR-TKIs treatment.

Patients number	Age/ sex	Pathological type of NSCLC	Initial stage	antecedent cytotoxic therapy	radiotherapy	EGFR-TKI treatment	Interval from EGFR-TKI treatment until leukemia	type of leukemia	Treatment for leukemia	Prognosis	Cause of death
1	49/ M	Adenocarcinoma	IV	yes	yes	Gefitinib(second-line treatment), 15 mo	15 mo	APL	all-trans retinoic acid; cytarabine/mitoxantrone	/	/
2	65/ M	Squamous cell carcinoma	IIIB	yes	yes	Gefitinib(second-line treatment), 25 mo	25 mo	APL	all-trans retinoic acid; cytarabine/ mitoxantrone; cytarabine/ daunorubicin; cytarabine/idarubicin	/	/
3	72/ M	Adenocarcinoma	IA	yes	yes	Gefitinib(second-line treatment), 5 mo + 4 mo (stopped and restarted)	26 mo	APL	all-trans retinoic acid	/	/
4	51/F	Adenocarcinoma	/	yes	yes	Gefitinib(second-line treatment), 14 mo	14 mo	APL	all-trans retinoic acid/ idarubicin/cytarabine	/	/
5	67/ M	Adenocarcinoma	IIIB	yes	yes	Erlotinib(second-line treatment), 4 mo	8 mo	MDS	cisplatin/gemcitabine	/	/
6	70/ M	Adenocarcinoma	IIIB	yes	yes	Erlotinib(second-line treatment), 8 mo	8 mo	CML	cisplatin/paclitaxel	/	/
7	60/F	Adenocarcinoma	IIIB	yes	yes	Erlotinib(third-line treatment), 8.5 mo	8.5 mo	MDS	vinorelbine/cisplatin; carboplatin/etoposide	Died 3.5 mo later	pneumonia
8	59/F	Squamous cell carcinoma	IV	yes	yes	Erlotinib(second-line treatment), 5.5 mo	5.5 mo	MDS	carboplatin/etoposide	Died 8 mo later	respiratory failure due to lung cancer progression
9	72/ M	Squamous cell carcinoma	II	yes	yes	Gefitinib	/	Acute megakaryoblastic leukemia	no further treatment	Being followed up	/
10	52/ M	Adenocarcinoma	IV	yes	yes	Erlotinib(third-line treatment), 11 mo	11 mo	AML	daunorubicin/ cytarabine; mitoxantrone/etoposide	Died of 10 mo later	reepiratory failure
11	45/ M	Adenocarcinoma	IIIA	no	no	osimertinib(first-line treatment), 8 mo	8 mo	CML	flumatinib	Being followed up	/

during EGFR-TKIs treatment. More epidemiological research and genetic experiments is needed to clarify whether EGFR-TKIs possess leukemogenic potential. For patients with CML during EGFR-TKIs treatment, osimertinib combined with flumatinib may represent an effective and well-tolerated treatment modality.

Ethical Statement

The patient provided **written informed** consent to this publication of all their data and images included. The authors are accountable for all aspects of the work. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

Data availability statement

Data associated with our study has not been deposited into a publicly available repository, and the data that has been used is confidential.

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CRediT authorship contribution statement

Libo Zhang: Writing – review & editing, Writing – original draft, Data curation. **Meijuan Huang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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