

## **Review 1**

Thank you for scrupulous review of our manuscript and valuable comments.

We have made additions and revised the manuscript per the points that you have made.

We made change according to the publication format of World Journal of Clinical Cases using subsections in CASE REPORT section.

Here are the responses to the comments. We hope the followings are those of what are to be supplemented.

- 1. The author should provide a clean version of the manuscript.**
- 2. Under the heading of Case Presentation, the following seven aspects must be presented in this order: 1) Chief complaints; 2) History of present illness; 3) History of past illness; 4) Personal and family history; 5) Physical examination; 6) Laboratory examinations; and 7) Imaging examinations.**
- 3. Please modify according to the annotation in the manuscript carefully.**

<reply>

We deleted the comments from our own peer review and submitted a clean version of the manuscript.

We added the heading of seven aspects on case presentation.

Authors made change of manuscript according to your recommendation and

marked it in **red color**.

**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript type:** CASE REPORT

**Therapy-related myeloid leukemia during erlotinib treatment in an NSCLC patient**

**Running Title:** T-AML during erlotinib treatment for NSCLC

The guidelines of the "CARE Checklist - 2016: Information for writing a case report" have been adopted

## Abstract

### BACKGROUND

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are tolerable drugs used for patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC). Serious adverse reactions are uncommon compared with cytotoxic drugs.

### CASE SUMMARY

A 52-year-old man presented with general weakness and cytopenia. He had been taking erlotinib for 11 months to treat NSCLC. The pathological diagnosis from the right upper lobe mass was adenocarcinoma with an EGFR mutation in exon 21 (L858R). He had previously received paclitaxel/carboplatin, gemcitabin/vinorelbine chemotherapy, stereotactic radiosurgery for brain metastasis, and whole-brain radiotherapy as treatment for NSCLC. We diagnosed the patient with acute myeloid leukemia (AML). During the induction and consolidation chemotherapy for AML, the erlotinib was discontinued. When complete remission of the AML was achieved, since the lung masses were increased, pemetrexed/cisplatin for the NSCLC was initiated. After two cycles of chemotherapy, the cytopenia was prolonged. AML relapse occurred with the same karyotype.

### CONCLUSION

Therapy-related acute myeloid neoplasm (t-MN) is a rare but fatal late complication. Although a patient may be taking EGFR-TKIs, the possibility of t-MN should be considered. Further studies are needed to determine whether EGFR-T

KI usage is a predisposing factor for t-MN.

**Key words:** Acute myeloid leukemia; Case report; Erlotinib; Protein Kinase

**Inhibitors; Neoplasm, second primary; Non-small cell lung cancer**

**Core tip:** Therapy-related acute myeloid leukemia (t-AML) developed during erlotinib treatment in a patient with epidermal growth factor receptor (EGFR)-mutant advanced non-small cell lung cancer (NSCLC). Alkylating cytotoxic drugs and radiotherapy are common treatments for patients with NSCLC. Cases of t-AML related to alkylating agents typically have a long latency period. Since it was 20 months in this case, EGFR-tyrosine kinase inhibitor (EGFR-TKI) usage may be related to or hasten AML development in patients who previously received cytotoxic chemotherapy. Although the mechanism remains unclear, when a patient takes an EGFR-TKI, t-AML development should be considered, especially if cytopenia persists.

## INTRODUCTION

Therapy-related acute myeloid leukemia (t-AML) is a rare but fatal late complication of cytotoxic chemotherapy. According to Surveillance, Epidemiology, and End Results data in US cancer registries, 18 patients with t-AML were identified in 2001–2008 among 37,008 non-small cell lung cancer (NSCLC) patients who received initial chemotherapy in adulthood<sup>[1]</sup>. Since patients with NSCLC receive multiple lines of treatment, it is difficult to determine which of the cytotoxic drugs are related to the AML that occurs several years later.

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the target therapy for patients with EGFR-mutant NSCLC. EGFR-TKIs are known to be relatively tolerable drugs for patients and less toxic than cytotoxic agents. Moreover, serious adverse reactions to them are uncommon<sup>[2]</sup>.

We identified a case of AML that developed during erlotinib treatment and reviewed cases of myeloid neoplasms that occurred during EGFR-TKI treatment in the literature.

## CASE PRESENTATION

### 1) Chief complaints

A 52-year-old man presented with general weakness. His symptoms had waxed and waned during the past several months.

### 2) History of present illness

He was under lung cancer treatment consisting of erlotinib 100 mg/day, levetiracetam 1000 mg/day, and prednisolone 10 mg/day to control his symptoms and prevent seizure that related with brain metastasis.

### 3) History of past illness

He had a medical history of chemotherapy and radiotherapy for NSCLC diagnosed as adenocarcinoma, T2bN2M1a by the International Association for the Study of Lung Cancer seventh edition guidelines 20 months prior. The pathological diagnosis of the right upper lobe mass was adenocarcinoma with an EGFR mutation in exon 21(L858R). As first-line chemotherapy, he received six cycles of combination paclitaxel (175 mg/m<sup>2</sup>) and carboplatin (AUC 4). At that time, EGFR-TKI was not covered by medical insurance benefits as the first-line therapy, so cytotoxic chemotherapy was administered. After disease progression occurred, he received three cycles of gemcitabine (1000 mg/m<sup>2</sup>) and vinorelbine (25 mg/m<sup>2</sup>) chemotherapy. He then developed memory problems and gait difficulties. Brain MRI revealed a brain metastasis. We decided to perform stereotactic radiosurgery using a Cyberknife to resect multiple metastatic lesions (total 23 Gy). Six months later, the size and number of brain metastatic lesi

ons had increased. He subsequently received whole-brain radiotherapy (total 30 cGy).

#### 4) Personal and family history

Our patient, who ran a flower shop, was a former smoker with a 26 pack-years history of smoking. He had quit smoking a year prior.

#### 5) Physical examination

His vital signs and physical examination findings were unremarkable except for a chronic ill-looking appearance.

#### 6) Laboratory examinations

A complete blood count revealed a white blood cell count of 7600 (absolute neutrophil count, 500), hemoglobin level of 12.4 g/dL, and platelet count of 83,000/ $\mu$ L. A leukocyte differential count revealed an absolute neutrophil count of 500/ $\mu$ L, lymphocyte count of 2400/ $\mu$ L, and monocyte count of 1000/ $\mu$ L. Immature cells were observed in the peripheral blood (Figure 2A). The chemistry results were normal except for a lactate dehydrogenase level of 293 U/L (reference interval, 106–211 U/L).

#### 7) Imaging examinations

In the initial diagnosis, chest computed tomography (CT) revealed a 61 mm  $\times$  44 mm lobulated mass in the right upper lobe and another 31 mm  $\times$  23 mm spiculated mass in the left upper lobe. As the third-line therapy, we started erlotinib, an EGFR-TKI, at a dose of 150 mg/day 11 months prior. During erlotinib treatment, the mass in the right upper lung became markedly improved (Figures 1A, B).

## **FINAL DIAGNOSIS**

Bone marrow aspirate smears revealed a monocytic blast rate of 77.3% (Figure 2B). Eosinophil levels in the bone marrow were increased (14.4%). A bone marrow biopsy revealed 80% cellularity. While megakaryocytes were decreased, immature cells diffusely infiltrated the bone marrow. CBFβ/MYH11 rearrangement was observed by fluorescence in situ hybridization analysis. On a chromosome analysis, inv(1) and inv(16) were detected. The patient's karyotype was 46, XY, inv(1) (p22q32), inv(16) (p13.1q22).

## **TREATMENT**

After receiving the diagnosis of AML, the patient started induction chemotherapy with daunorubicin/cytarabine and consolidation chemotherapy with high-dose cytarabine. During AML treatment, the erlotinib treatment was stopped.

## **OUTCOME AND FOLLOW-UP**

At the time that complete remission of the AML was achieved, both upper lobe masses had increased in size (Figure 1C). Fourth-line chemotherapy with pemetrexed/cisplatin for NSCLC was initiated. After two cycles of chemotherapy, the cytopenia persisted. The complete blood count revealed a white blood cell count of 1800 (absolute neutrophil count, 972), hemoglobin level of 9.6 g/dL, and platelet count of 88,000/ $\mu$ L. Immature cells were observed in the peripheral blood. The

result of the bone marrow study was AML relapse with the same karyotype. Re-induction chemotherapy with mitoxantrone/etoposide did not achieve remission. We administered low-dose cytarabine chemotherapy; the patient was exhausted with poor performance status and died of respiratory failure 10 months after receiving the AML diagnosis.

## DISCUSSION

This case involved t-AML that developed during erlotinib treatment in a patient with NSCLC. The case was considered a therapy-related myeloid neoplasm rather than de novo AML because the patient had a clinical history of antecedent cytotoxic therapy and radiotherapy. Carboplatin and radiotherapy in this patient were risk factors for t-AML<sup>[3]</sup>. Patients with t-AML related to alkylating agents generally experience a longer latency period (5-7 years) than those with t-AML related to topoisomerase-2 inhibitors (2-3 years) between therapy and myeloid neoplasm development<sup>[4]</sup>. This can predict the long interval between alkylating chemotherapy and an AML diagnosis. However, in the present case, the interval between the initiation of carboplatin treatment and AML development was 20 months, which was relatively short.

Differentiating t-MN from de novo myelodysplastic syndrome (MDS)/AML is difficult because mutation profiling has demonstrated similar abnormalities for both conditions. Common patterns in recurrent mutations and chromosomal abnormalities are chromosome 5 and 7 loss with alkylating agent exposure and *MLL* translocations at 11q23 or *RUNX1/AML1* at 21q22 with topoisomerase-2 inhibitor exposure<sup>[4,5]</sup>. However, de novo and therapy-related MDS/AML can share genetic features (especially the 11q23 anomaly). There are no pathognomonic morphologic or genetic features of t-MN<sup>[5]</sup>.

EGFR-TKIs are the current first-line treatment for patients with EGFR mutation-positive advanced NSCLC. There have been a few reports related to leukemia and

EGFR-TKIs<sup>[6-9]</sup>. In the literature review (Table 1), we identified eight patients with t-MN after EGFR-TKI treatment for antecedent NSCLC. The mean interval from the first-line NSCLC treatment to AML development was 40.7 (range, 11-120) months. None of the patients who were diagnosed with t-MN after EGFR-TKI treatment for NSCLC had taken topoisomerase II inhibitors. Since the latency period for these patients was not longer than expected, we considered the possibility that EGFR-TKI might be associated with the development of myeloid neoplasms.

The duration of EGFR-TKI therapy before AML was relatively short (mean, 13.4 months; range, 5.5-26 months). However, since cytotoxic chemotherapy drugs were administered prior to EGFR-TKI in all of these patients, the development of myeloid neoplasm may be related to both classes of drugs. It was not known whether the occurrence of t-MN was different depending on the type of EGFR mutation. This is because out of the 8 reported cases, only our case (L858R) provided the type of EGFR mutation.

Several case reports have shown that EGFR-TKIs might have leukemogenic effects in patients with t-MN after the administration of EGFR-TKIs<sup>[6,8,10]</sup>. However, after EGFR-TKIs were commercially approved, to the best of our knowledge, no cases of myeloid neoplasms after the administration of EGFR-TKI alone for NSCLC treatment have been reported in the literature. All patients of case reports with t-MN received chemotherapy or radiotherapy for NSCLC treatment before receiving EGFR-TKIs. We suggest that EGFR-TKI may be related to or shorten the interval to AML development when patients previously received cytotoxic chemotherapy. According to the historical concept, cytotoxic drugs such as topoisomerase II

inhibitors or radiotherapy induce DNA damage that leads to translocation. In the model for the role of clonal selection<sup>[4]</sup>, clonal hematopoiesis of indeterminate potential (CHIP) is characterized by the absence of morphological evidence of disease and the presence of a clonal population of hematopoietic cells with somatic mutations in the genes associated with hematologic malignancies<sup>[11]</sup>.

Toxins, drugs, oligoclonality with aging, chemoradiation, chemical exposure, immune destruction, or dysfunctional hematopoiesis may be selected for mutant clones and induce CHIP. Additional somatic alterations in CHIP can promote high-risk myeloid neoplasms. We considered the possibility that certain effects of EGFR-TKI on the tyrosine kinase pathway could play a role in CHIP.

Long-term epidemiological research is needed to clarify whether there is a relationship between EGFR-TKI treatment and the rare but serious events noted here. If the incidence of this complication in the EGFR-TKI-treated cohort is beyond that expected on the basis of patients with NSCLC before EGFR-TKIs are commercially available, we must consider EGFR-TKIs as the predisposing factor of t-MN.

## CONCLUSION

In summary, if cytopenia persists in patients treated with EGFR-TKIs for NSCLC, the possibility of t-MN should be considered. Further studies are needed to determine whether the administration of EGFR-TKIs is a predisposing factor for t-MN.



### **Conflict of interest**

No potential conflicts of interest relevant to this article are reported.

### **ACKNOWLEDGEMENTS**

This work was supported by the Soonchunhyang University Research Fund.

**IRB approval** for waiver of informed consent. (IRB file number: SCHUH 2021-02-030)

### **Author Contributions**

Koo SM and Kim KU designed research; Koo SM, Kim KU, Kim YK, and Uh ST performed research, analyzed data, and wrote the paper. All authors have read and approve the final manuscript.

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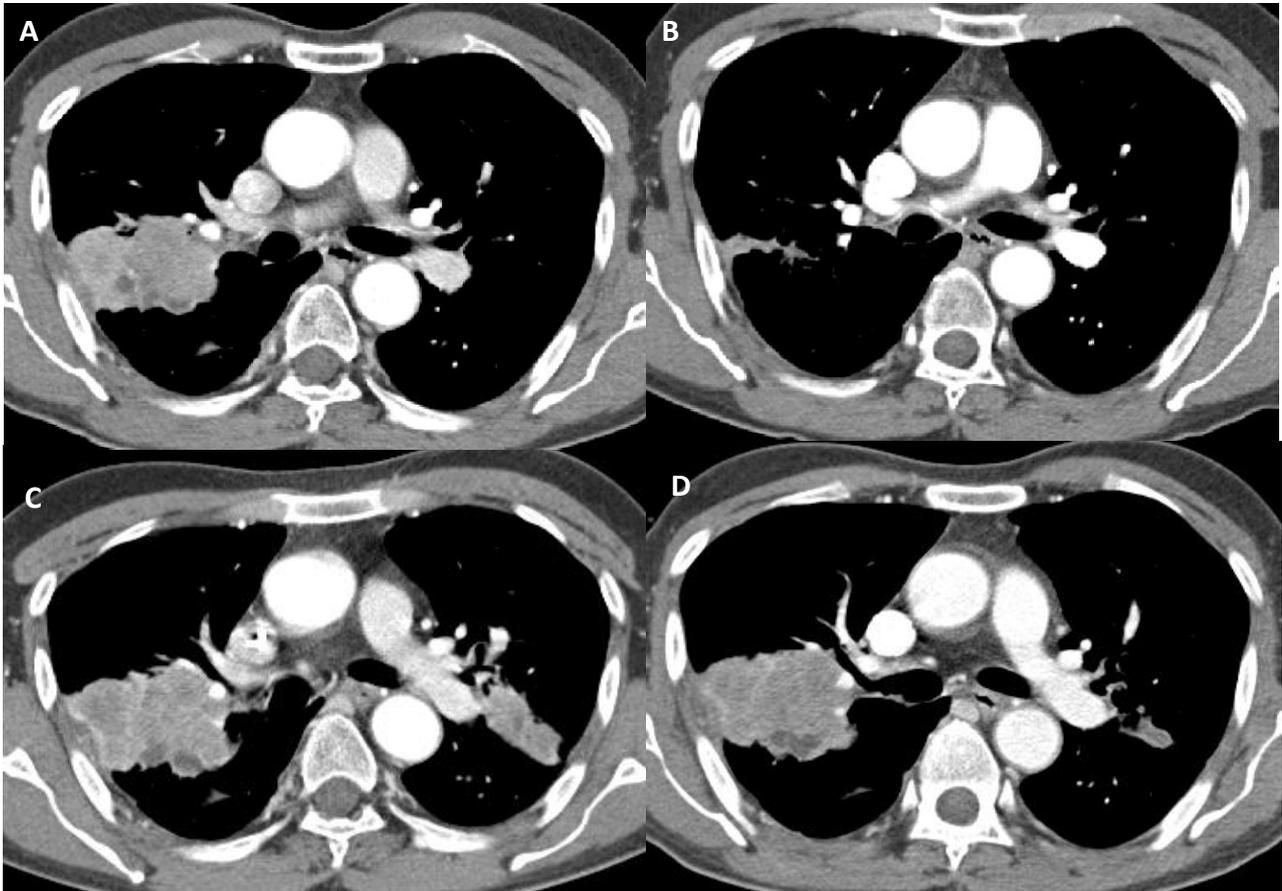
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## Figures and legends

### Figure 1. Contrast-enhanced chest computed tomography findings

A: Before erlotinib treatment, a 59 mm × 42 mm heterogenous enhancing lobulated mass in the right upper lobe (RUL) is closely abutting the adjacent costal pleura with focal thickening and retraction. B: During erlotinib treatment, the mass in the RUL is markedly improved. C: Four months after discontinuing the erlotinib due to leukemia induction chemotherapy, the mass in the RUL is enlarged, and a spiculated mass is visible in the left upper lobe (LUL) (24 mm × 17 mm). D: Two months after pemetrexed/cisplatin treatment, no remarkable changes in the RUL and LUL masses are noted.



**Figure 2. Blood smear and bone marrow aspiration results**

A: The blood smear shows 44% blast cells ( $\times 1000$ ). B: The bone marrow aspiration showed 77.3% myoblasts ( $\times 1000$ )

**A**

**B**

## Table

Table 1. Literature review findings of therapy-related myeloid neoplasms after EGFR-TKI treatment in NSCLC patients

Patient number	Author (published year)	Age/sex	Pathological type of NSCLC	Initial stage	EGFR mutation	Prior chemotherapy	Interval from first line treatment	Prior radiotherapy	Duration of EGFR-TKI treatment	Interval from EGFR-TKI treatment until leukemia	CBC profiles at leukemia presentation: WBC(ANC)( $\mu$ l)-hemoglobin(g/dL)/hematocrit(%)-platelets/mL	Characteristics (Karyotype) of leukemia/MD S	Survival after diagnosis of leukemia
1	Uchida, et al (2005)	49/M	Adenocarcinoma	IV(T1N0M1)	NA	Cisplatin/docetaxel/irinotecan 2 cycles	36 months	Cyberknife for brain metastasis (22.993Gy)	Gefitinib 15months	15months	NA	APL Normal karyotype, PML RAR $\alpha$ positive	NA
2	Uchida, et al (2005)	65/M	Squamous cell carcinoma	IIIB(T4N3M0)	NA	Cisplatin/mitomycin/vinorelbine 2 cycles, Uracil/tegafur for 2 months in adjuvant setting	48 months	Fractionated radiotherapy (2Gy* 25)	Gefitinib 25months	25months	NA	APL Normal karyotype, PML RAR $\alpha$ positive	NA
3	Uchida, et al (2005)	72/M	Adenocarcinoma	IA(T1N0M0)	NA	Carboplatin/paclitaxel 1 cycle, Cisplatin, carboplatin, irinotecan, docetaxel, gemcitabine, vinorelbine, paclitaxel, amrubicin	69 months	None	Gefitinib 5 months + 4months (discontinued and restarted)	26months	NA	APL Normal karyotype, PML RAR $\alpha$ positive	NA
4	Ennishi, et al (2006)	51/F	Adenocarcinoma	Recurrence after LLL lobectomy, mediastinal LN metastasis	NA	Carboplatin/paclitaxel 6 cycles	NA	Radiotherapy at a total dosage of 60 Gy	Gefitinib 14 months	14months	2300-13.2/-15,200	APL t(15;17)(q22;q21), PML/RAR $\alpha$ positive	NA
5	Stathopoulos, et al (2010)	67/M	Adenocarcinoma	IIIB	NA	Cisplatin/gemcitabine 6 cycles	11 months	None	Erlotinib 4 months	8 months	grade 4 thrombocytopenia	MDS 46,XY,del(20)(q11)[15]/47,idem,+21(7)/48,idem,21,+21[-3]	NA
6	Stathopoulos, et al (2010)	70/M	Adenocarcinoma	IIIB	NA -	Cisplatin/paclitaxel 6 cycles	12 months	None	Erlotinib 8 months	8 months	WBC 92,000	CML BCR-ABL+	NA
7	Stathopoulos, et al (2010)	60/F	Adenocarcinoma	IIIB	NA	Cisplatin/vinorelbine 6 cycles Carboplatin/etoposide 3 cycles	36 months	Radiotherapy (RT) of the primary lung lesions and of the mediastinum	Erlotinib 8.5 months	8.5 months	2500-/28.8-72,000	MDS, RAEB-T/t-AML 46,XX,del(7)(q22),add(21)(q22)	Died 3.5 months later
8	Stathopoulos, et al (2010)	59/F	Squamous cell carcinoma	IV	NA	Carboplatin/etoposide 6 cycles	14 months		Erlotinib 5.5 months	5.5 months	3200-/25.7	MDS, RAEB 47,XX,+8,t(5;9)(q13;q34)	Died 8 months later
9	Moon, et al (2014)	72/M	Squamous cell carcinoma	II(T2N1M0)	NA	a combination of radiotherapy and a repeated chemotherapy regimen (4 trials, 13 cycles) consisting of docetaxel, cisplatin, gemcitabine, vinorelbine, gefitinib, irinotecan, and carboplatin	10 years	Combination of radiotherapy and a repeated chemotherapy regimen	Gefitinib, Duration:NA	NA	1700 (780)-5.2/-34,000	T-AML (Acute megakaryoblastic leukemia) -5,-7,+2mar	being followed up
10	Present case	52/M	Adenocarcinoma	IV(T2bN2M1a)	L858R	Paclitaxel/carboplatin 6 cycles, gemcitabine/vinorelbine 3 cycles	20 months	Cyberknife for brain metastasis (23Gy), WBRT (30Gy)	Erlotinib 11 months	11 months	7600(500)-12.4/-83000	AML 46, XY, inv(1) (p22q32), inv(16) (p13.q22)	Died 10 months later

APL, acute promyelocytic leukemia; ANC, absolute neutrophil count; CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; MDS, myelodysplastic syndrome; NA, not applicable; NSCLC, non-small cell lung cancer; RAEB-T, refractory anemia with excess blasts in transformation; t-AML, therapy-related acute myeloid leukemia; WBC, white blood cell

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**Review 2**

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