TYROSINE KINASE INHIBITOR RESISTANCE IN NON SMALL CELL LUNG CARCINOMA SUBTYPE ADENOCARCINOMA PATIENT WITH POSITIVE EPIDERMAL GROWTH FACTOR RECEPTOR

Angelin Utami Cahyani1, Eko Budiono2
1Resident ofInternal Medicine Departement of UGM Medical Faculty/Dr. Sardjito Hospital Yogyakarta
2Pulmonology Division of internal Medicine Departement of UGM Medical Faculty/Dr. Sardjito Hospital Yogyakarta
1Departemen Ilmu Penyakit Dalam FKUNSRI/RSMH Palembang
2Divisi Pulmonologi Departemen Ilmu Penyakit Dalam FKUNSRI/RSMH Palembang

ABSTRACT

The found of Epidermal Growth Factor Receptor (EGFR)mutation in patient with Non Small Cell Lung Carcinoma (NSCLC) began the personalized therapy in treatment management of NSCLC. Since discovered 10 years ago, EGFR mutation which was response to Tyrosine Kinase Inhibitor (TKI) such asgefitinib, there was also found that the condition in which that therapy was resisted. Mutation in exon 20 insertion that leads to poor signaling of EGFR inhibition is associate with oncogenic trasnformation which is resistance to TKI. This case will be disscused to know if there is any resistance to TKI that need to be treated by other strategy.

Keywords: Lung Cancer, Non Small Cell Lung Carcinoma, Adenocarcinoma, Epidermal Growth Factor Receptor, Tyrosine Kinase Inhibitor, Gefitinib, Iressa

Case Presentation

A 42 year old woman was diagnosed with NSCLC with Adenocarcinoma subtype, metastation process in vertebrae, hospital acquired pneumonia, suspect of MESCC, pleural efussion due to malignancy, and antral erosive gastritis. Diagnosis of NSCLC with adenocarcinoma subtype based on cytology examination of pleural efusionwhich found a malignant cell refer to NSCLC with adenocarcinoma subtype. Result from EGFR examination at Desember 7, 2016, found that there was a mutation in exon 19 (deletion) and 20 (insertion). Patient then was treated with Gefitinib 250 mg per oral once a day. There was no any positive progression of diseases until she died.

Disscusion

Chemotherapy was standard therapy in advance stage of NSCLC in previous decade. Discovered of Epidermal Growth Factor Receptor (EGFR) mutation began the personalized/targeted therapy in NSCLC and those thing has changed the point of view about its therapy. NSCLC therapy based on EGFR mutation which responded to TKI therapy (gefitinib, erlotinib, and afatinib) has began since 10 years ago. It is still challenging even after the discovered of new NSCLC therapy, that is the potentiality of resistance from TKI therapy.

Several study concluded that mutation with insertion type at exon 20 in EGFR gene was associated with oncogenic transformation which resisted to TKI. In vitro study showed that gefitinib couldn't inhibit EGFR signaling proscess in patient with exon 20 mutation, continued cell proliferation and anti apoptosis mechanism. Other mechanism that probably contributes to TKI resistence is secondary resistance mechanism, that is mutation at T790M in EGFR gene, produces inhibition of TKI to adhere to EGFR receptor.However, the real mechanism of it is still unkown and still under the study

Address for Correspondance : **Angelin Utami Cahyani, Eko Budiono**
Email: angelinutami@yahoo.com

How to cite this article :

TYROSINE KINASE INHIBITOR RESISTANCE IN NON SMALL CELL LUNG CARCINOMA SUBTYPE ADENOCARCINOMA PATIENT WITH POSITIVE EPIDERMAL GROWTH FACTOR RECEPTOR

Case Presentation

A 42 year old woman was diagnosed with NSCLC with Adenocarcinoma subtype, metastation process in vertebrae, hospital acquired pneumonia, suspect of MESCC, pleural efussion due to malignancy, and antral erosive gastritis. Diagnosis of NSCLC with adenocarcinoma subtype based on cytology examination of pleural efusionwhich found a malignant cell refer to NSCLC with adenocarcinoma subtype. Result from EGFR examination at Desember 7, 2016, found that there was a mutation in exon 19 (deletion) and 20 (insertion). Patient then was treated with Gefitinib 250 mg per oral once a day. There was no any positive progression of diseases until she died.

Disscusion

Chemotherapy was standard therapy in advance stage of NSCLC in previous decade. Discovered of Epidermal Growth Factor Receptor (EGFR) mutation began the personalized/targeted therapy in NSCLC and those thing has changed the point of view about its therapy. NSCLC therapy based on EGFR mutation which responded to TKI therapy (gefitinib, erlotinib, and afatinib) has began since 10 years ago. It is still challenging even after the discovered of new NSCLC therapy, that is the potentiality of resistance from TKI therapy.

Several study concluded that mutation with insertion type at exon 20 in EGFR gene was associated with oncogenic transformation which resisted to TKI. In vitro study showed that gefitinib couldn't inhibit EGFR signaling proscess in patient with exon 20 mutation, continued cell proliferation and anti apoptosis mechanism. Other mechanism that probably contributes to TKI resistence is secondary resistance mechanism, that is mutation at T790M in EGFR gene, produces inhibition of TKI to adhere to EGFR receptor.However, the real mechanism of it is still unkown and still under the study

Some strategy to solve the intrinsic resistence mechanism are :

1. Switch the therapy programe into cytotoxic chemotherapy,

which is the only one therapy in TKI intrinsic resistence

2. The use of 3 rd EGFR TKI therapy (dacomtinib, osimertinib)
3. Comprehensive genetic analysis to find deletion in exon 20 or substitution in T790M
4. A new therapy that work in pathways which is activated by EGFR, so can be expected that proliferation of cell doesn't occur even EGFR still activated

Conclusion

Has been reported, a 42 year old women diagnosed with Non Small Cel Lung carcinoma (NSCLC) with Adenocarcinoma subtype, which was metastated to vertebrae, hospital acquaired pneumonia, suspect of MESCC, pleural effusion due to malignancy and erosive antral gastritis. This patient diagnosed with NSCLC with adenocarcinoma subtype based on cytological examination from pleural effusion. From EGFR examination there was a mutation detected on exon 19 (deletion), and 20 (insertion). This patient then treated with Gefitinib 1 x 250 mg per oral once a day. There was no clinical improvement until finally she died.

Study showed that insertion in exon 20 which led to oncogenic transformation was associate with TKI resistence due to poor signalling EGFR inhibition which was proof on in vitro study. This problem need to be solved with other treatment strategy like chemotherapy, EGFR therapy witht TKI 3rd generation, comprehensive genetic analisys to know the mutation (deletion) in exon 20 and subtitution of T790M and new theraphy modalities that work in pathway which is activated by EGFR.

References

1. Li, M., 2016. Role of gefitinib in the targeted treatment of non- small-cell lung cancer in Chinese patients. , pp.1291-1302.
2. Park, K. et al., 2014. Safety and Efficacy of Dacomitinib in Korean Patients with KRAS Wild-Type Advanced Non - Small-Cell Lung Cancer Refractory to Chemotherapy and Erlotinib or Gefitinib. Journal of

Thoracic Oncology, 9(10), pp.1523-1531. Available at: http://dx.doi.org/10.1097/JTO.0000000000000275.

3. Wang , 2016. Intrinsic resistance to EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer with activating EGFR mutations. , pp.3711-3726.
4. Russo, A. et al., 2015. A decade of EGFR inhibition in EGFR-mutated non small cell lung cancer (NSCLC): Old successes and future perspectives. , 6(29).
5. Wang, X., Goldstein, D. & Crowe, P.J., 2016. Next-generation EGFR / HER tyrosine kinase inhibitors for the treatment of patients with non-small-cell lung cancer harboring EGFR mutations : a review of the evidence. , pp.5461-5473.