International Journal of Scientific Research Updates

Journal homepage: https://orionjournals.com/ijsru/

ISSN: 2783-0160 (Online)

(CASE REPORT)

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Triple positive lung cancer: A case report

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International Journal of Scientific Research Updates, 2022, 03(01), 029–033

Publication history: Received on 18 December 2021; revised on 24 January 2022; accepted on 26 January 2022

Article DOI: https://doi.org/10.53430/ijsru.2022.3.1.0023

Abstract

Background: Targeted therapies in nonsmall cell lung cancer has changed the landscape of management and carved the disease in to more different sub types. Despite of considerable initial response to 1st generation and 2nd generation tyrosine kinase inhibitors patients develop resistance in the due course. Secondary mutations are due to threonine and methionine substitution at 790 (T790M) of EGFR. T790M mutation are resistant to 1st and 2nd generation TKI.Osimertinib is a irreversible third generation epidermal growth factor receptor tyrosine kinase inhibitor effective against EGFR T790M mutation positive lung cancer. Patients are inescapable of developing resistance with Osimertinib in spite of initial response and leaving no further definite therapeutic options. In 20-30% patients with osimertinib resistance develop EGFR C797S mutation. Our objective is to show the patient journey with primary, secondary mutation withT790M and tertiary mutation in C797S.

Key Messages: Prospective molecular tumor profiling is now the standard of care in the treatment of metastatic NSCLC. Re-biopsy or liquid biopsy on progression of first and second line TKI to look for T790M has already been in routine practice. Re-biopsy or liquid biopsy on progression of third line TKI and molecular profiling can guide us in further management.

Keywords: T790M Mutation; Tertiary mutation in Lung cancer; EGFR mutations; Triple positive lung cancer; C797S Mutation

1 Introduction

Non-small-cell lung cancer (NSCLC) is one of the leading causes of cancer related deaths [1]. Tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR) are effective in management of advanced NSCLC with primary mutations in EGFR gene. Major challenge is acquired resistance to the first line TKIs [2,3]. The second-generation EGFR TKIs have shown promising response in some and many of them eventually develop resistance. It is prudent to do re biopsy or a liquid biopsy at the time of clinical progression to detect newer mutations. These acquired molecular alterations are associated with resistance to 1st and 2nd generation TKI treatment. The most important mechanisms of resistance is development of secondary mutation, T790M mutation in exon 20. It is acquired in about 50% of cases following 1st generation TKI treatment. Osimertinib is a third-generation covalent EGFR inhibitor that targets both the sensitizing EGFR mutations as well as EGFR mutation with T790M. Patients treated with Osimertinib also develop resistance attributable to acquired molecular alterations. Resistance mechanisms identified to third-generation EGFR TKIs(Osimertinib) include acquired EGFR C797S mutation (C797 is the site at which osimertinib binds to the EGFR kinase domain), Loss of EGFR T790M, MET and HER2 amplification, YES1 amplification, and acquired mutations, including KRAS, PIK3CA, and HER2 are the molecular alterations seen following Osimertinib treatment.

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2 Case History

A 58 yr old male presented with history of cough with expectoration and breathing difficulty of 1 month in may 2020. He was diagnosed to have adenocarcinoma of the left lung with mediastinal lymphadenopathy, parenchymal nodules in both lungs (stage IV). His molecular test revealed EGFR exon 19 deletion(L858R) and raised serum CEA 54 ng/ml. The patient was treated with Tab Erlotinib150 mg once daily for 18 months. Patient achieved complete response with normal serum CEA. After 18 months of treatment with Erlotinib there were signs of progression. The serum CEA was 54 ng/ml and FDG avid nodules in both lobes of lung (Fig-1). The patient was given 6 cycles of chemotherapy. Imaging was done to assess the disease after 6 cycles of chemotherapy showed persistent lung nodules and the serum CEA 45 ng/ml was elevated.

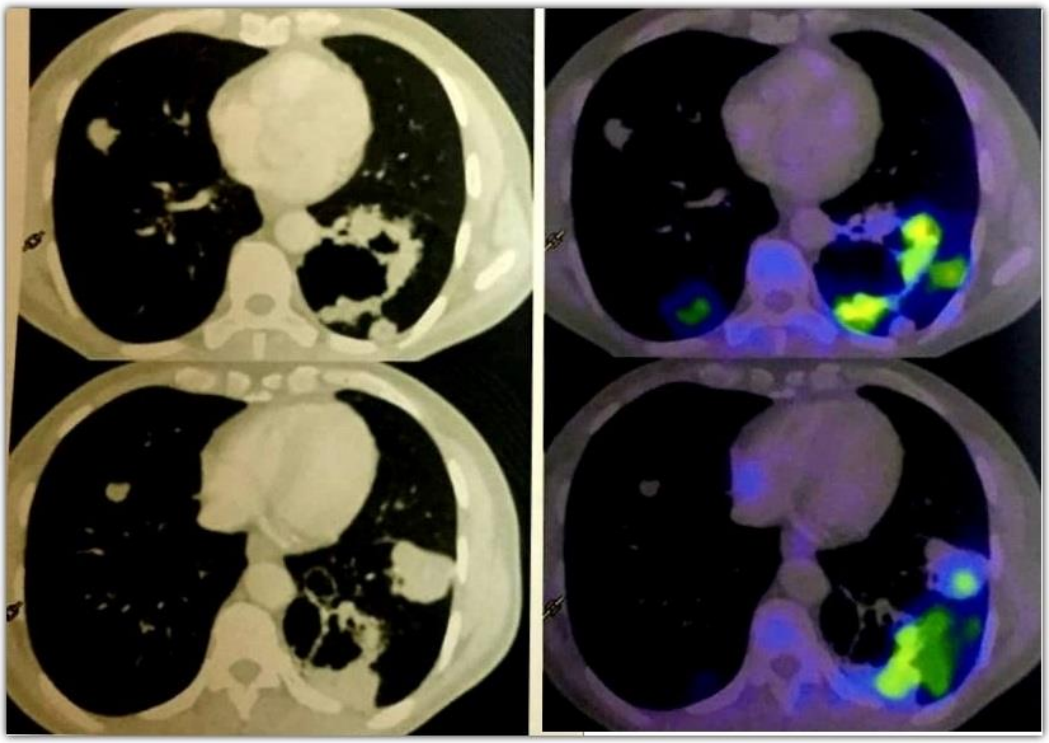

Figure 1 FDG PET CT showing disease extent at the start of Osimertinib

The patient's serum CEA was surrogate of the disease in this case. The patient was started on 2nd generation TKI (Tab Afatinib 40 mg once daily) and there was no conspicuous response to treatment.

As he failed to show any response to chemotherapy and second generation TKI re-biopsy from the lung lesion was done [4,5]. Histopathological diagnosis was undifferentiated carcinoma withnew Mutation T790M on exon 20 and deletion in exon 19(Fig 3). Patient was started on Tab Osimertinib 80 mg once daily.which was tolerated well and there was good radiological response on CT scans(Fig-2) and serum CEA was came back to normal value. Patient continued Osimertinib for 30 months. After 30 months of therapy with osimertinib, the lesions in left lower lobes were increased in size and serum CEA raised to 61.8 ng/ml. The patient underwent biopsy following progression on therapy. After biopsy patient was found to acquired third mutation C797S, T790M and exon 19 deletion (Fig4). This individual has primary mutation, secondary mutation and tertiary mutation that is Triple positive lung cancer.

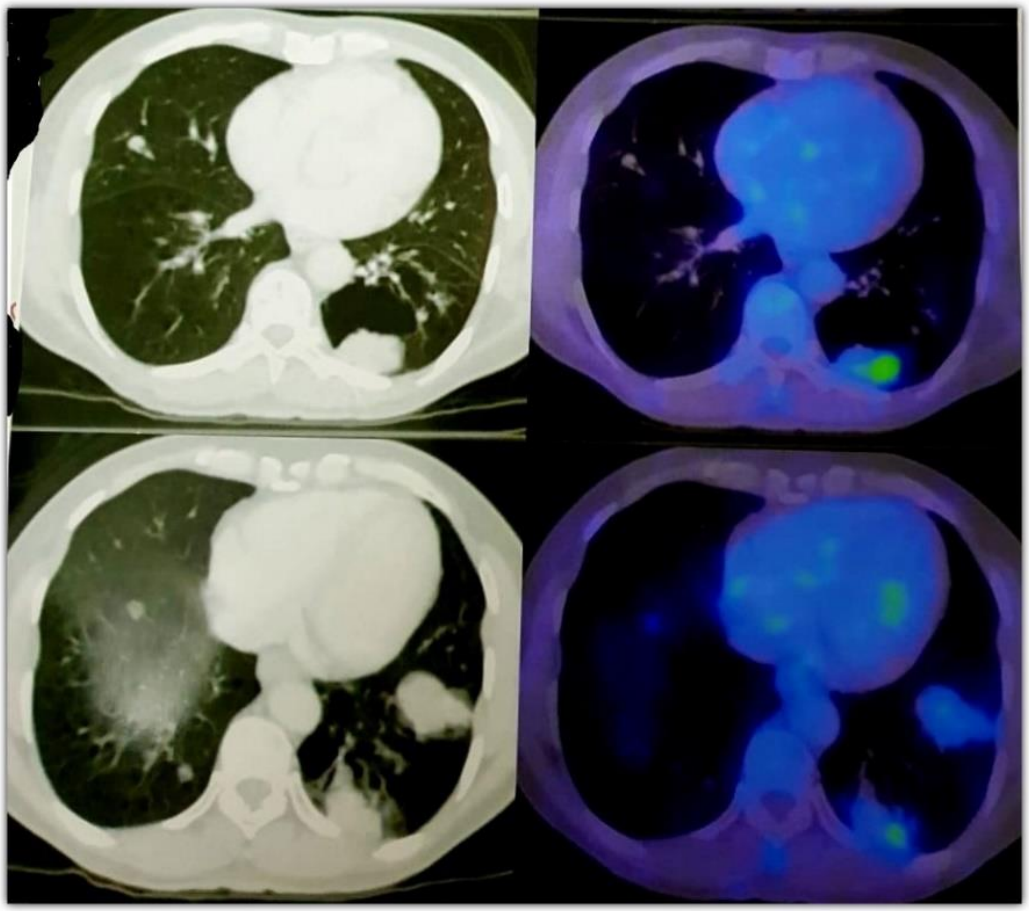

Figure 2 FDG PET CT showing good response at 24 months on Osimertinib

Result Summary:

Analysis for: Hotspot mutations – G719x, S768I, deletions in exon 19, T790M, insertions in exon 20, L858R and L861Q of the EGFR gene .

Mutations detected:

Sl.No	Mutation Tested	Exon No:	Ct value	ΔCt cut off	Mutation status	Clinical relevance
1	G719X 3substitutions	18	Undetermined	< 8.90	Negative	NA
2	Deletions (19 deletions)	19	26	< 8.0	Positive	Yes
3	S768I	20	Undetermined	< 8.90	Negative	NA
4	T790M	20	28	<7.40	Positive	Yes
5	Insertions (3 insertions)	20	Undetermined	< 8.0	Negative	NA
6	L858R	21	Undetermined	< 8.90	Negative	NA
7	L861Q	21	Undetermined	< 8.90	Negative	NA

Figure 3 Molecular profiling on re-biopsy after progression on 2nd line TKI

T790M, C797S and Exon 19 (Deletion) mutations were detected in *EGFR* gene of the subject

Clinically relevant gene fusions were not detected in this subject

ABLE 1: GENOMIC ALTERATIONS THAT CAN BE TARGETED WITH APPROVED DRUGS IN THE SUBJECT'S TUMOR TYPE

Gene	CDS variant#	Amino acid Change / Exon No.	Overall Depth / Mutant Allele Percentage	Approved drugs against variant	Drug response	Hot spot Mutation	Function of the gene in cancer
EGFR	c.2239_2251delinsC (ENST00000275493.2)	p.Leu747_Thr751delinsPro / Exon 19	4385X / 54%	Osimertinib / Gefitinib / Erlotinib / Afatinib / Dacomitinib	Good sensitivity to *EGFR* TKIs	YES	Oncogene
EGFR	c.2369C>T (ENST00000275493.2)	p.Thr790Met / Exon 20	8665X / 44.7%	Osimertinib (Third generation TKI)	Resistance to first / second generation TKIs	YES	Oncogene
EGFR	c.2389T>A (ENST00000275493.2)	p.Cys797Ser / Exon 20	8113X / 20.1%	NA	Resistance to Osimertinib	YES	Oncogene

Figure 4 Molecular profiling on re-biopsy after progression on 3rd line TKI

3 Discussion

The most prevalent mechanisms of acquired EGFR-TKI resistance are the EGFR T790M mutation, PIK3CA mutation, MET amplification and EMT . In present case, molecular test for primary tumor demonstrated existence of TKI sensitive mutation and it indeed obtained good response to Erlotinib. The presence of T790M mutation in recurrent lesions may explain the EGFR-TKI resistance reasonably because of the lacking of T790M mutation in the original lesions. Most distinct feature of the recurrent tumor was poorly differentiated tumor. Patient had excellent response to Osimertinib for 30 months. He acquired EGFR C797Smutation and developed resistance to osimertinib. As the patient has C797S the options are very limited he was given option of chemotherapy with Osimertinib + Gefitinib. The total journey of this patient is about 11 years and it is hard to believe a patient with metastatic lung cancer survived for this long.

Concerning triple-mutant EGFR NSCLC (activating-mutation/T790M/C797S), new avenues for treatment strategies have been hypothesized from preclinical studies. A newC797S mutant-selective inhibitor EAI045 has shown encouraging preclinical activity in combination with cetuximab, but only in patients with EGFR L858R activating mutation [6,7]. when C797S emerged in trans of the T790M allele, tumors remain sensitive to first- and third generation EGFR-TKI combinations, whereas tumors remain broadly resistant if C797S emerged in the cis position of T790M allele. A cis allelic position of C797S mutation with the T790M allele was observed in 66% (8/12) of cases (with available information), supporting

the clinical relevance of this EGFR-TKI combination strategy.New combinations are being assessed both in the first-line setting and after progression on Osimertinib to attempt to prevent and reverse resistance to Osimertinib, respectively. The combination of Osimertinib and Savolitinib, an MET inhibitor, has shown activity in patients with *MET* amplification after EGFR TKI therapy with Erlotinib, Afatinib, Gefitinib, or Osimertinib. Other combinations that are being assessed include Osimertinib and Bevacizumab, Osimertinib and Selumetinib, Osimertinib and Dasatinib among others.

4 Conclusion

Prospective molecular biology is now the standard of care in treatment of non-small cell lung cancer. Re biopsy of progressive disease, if possible, otherwise liquid biopsy to look for any new mutation especially T790M after 1st line targeted therapies. Patients progressing on Osimertinib needs further evaluation of new mutations to modify the treatment.

Compliance with ethical standards

Acknowledgments

We would like to thank our oncology team , Lab medicine department of the institute for helping us to do this case study. We would like to thank all the patients who are part of this study.

Disclosure of conflict of interest

We declare that there is no conflict of interest regarding this study.

Statement of informed consent

Informed written consent was taken from patient's next of kin (Son).

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