Irish Journal of Medical Science (1971 -) (2019) 188:405–408
https://doi.org/10.1007/s11845-018-1868-0

ORIGINAL ARTICLE

Co-occurrence of EGFR sensitising and resistance mutations at diagnosis in NSCLC

Deirdre Kelly[1] · Louise Burke[1] · Cathal O'Brien[2] · Rachel Kearns[1] · Shareen Rafee[1] · Derek Power[1] · Seamus O'Reilly[1] · Deirdre O'Mahony[1] · Richard Bambury[1]

Received: 14 June 2018 / Accepted: 10 July 2018 / Published online: 20 July 2018

Abstract

Background De novo epidermal growth factor receptor (EGFR) resistance mutations in tyrosine kinase inhibitor-naïve patients are rare when assessed by standard genotyping methods.

Methods Patients with EGFR mutations were identified using PCR-based fragment length analysis, mass spectrometry-based genotyping (Sequenom), and Sanger sequencing.

Results From 2008 to 2015, we observed de novo EGFR resistance mutations in 12.8 patients who received an EGFR TKI with an overall response rate of 25%, median PFS 24 months, and median OS 34 months. Five patients (63%) received erlotinib in the first-line setting with a 60% disease control rate (DCR) and a median duration of response of 6 months (range 4–45 months). Three (37%) received cytotoxic chemotherapy in the first-line setting with 67% DCR and a median duration of response of 11 months (range 10–12 months). In patients with de novo EGFR T790M mutations, 50% (2/4) had stable disease with one patient having an ongoing response to erlotinib of over 96 months. In patients with de novo EGFR S768I mutations who received erlotinib, 50% (2/4) have ongoing partial responses at 30 and 6 months.

Conclusion This is the largest Irish review of de novo synchronous EGFR mutations. The incidence of co-occurring EGFR mutations in our cohort of non-small cell lung carcinoma (NSCLCA) is 1% on routine assays. Erlotinib appears to have activity in this cohort in both in the first- and second-line setting. De novo S768I and T790M represent distinct clinical entities. For de novo T790M mutations cytotoxic chemotherapy may still be considered first line. For de novo S768I mutations, erlotinib appears to be a reasonable therapeutic option.

Keywords EGFR mutations · Erlotinib · S768I mutation · T790M mutation · Tyrosine kinase inhibitor

Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. An improved understanding of the molecular pathways that drive malignancy in non-small cell lung carcinoma (NSCLC) has led to the development of agents that target specific molecular pathways in malignant cells. Epidermal growth factor receptor (EGFR) is a cell surface receptor that activates tyrosine kinase activity. In malignancy, the receptor can be mutated to a constitutively active form leading to uncontrolled cell proliferation and metastasis.

International guidelines recommend testing for activating *EGFR* mutations in all patients with advanced non-squamous NSCLC [2, 3]. In advanced NSCLC, the presence of an activating *EGFR* mutation confers a more favourable prognosis and predicts for sensitivity to EGFR tyrosine kinase inhibitors (TKIs) in these patients [4].

Ninety percent of activating *EGFR* mutations occurs in exon 19 or at L858R. Ten percent of *EGFR* mutations occurs within exon 18–21 and the clinical characteristics as well of the therapeutic effects of EGFR TKIs within this group remain unclear [5].

There are a subset of *EGFR* mutations which confer resistance to TKI therapy, most commonly T790M and S768I.

✉ Deirdre Kelly
deirdre.kelly.2108@gmail.com

[1] Department of Medical Oncology, Cork University Hospital, Cork, Ireland

[2] Department of Pathology, Trinity Collage Dublin, Dublin, Ireland

Table 1 Clinical characteristics

	N (%)
Total	12
Age at diagnosis	
Median	65
Range	52–79
Stage at diagnosis	
I–II	1 (8%)
III	1 (8%)
IV	10 (83%)
Sex	
Men	4 (33%)
Women	8 (67%)
Histology	
Adenocarcinoma	12 (100%)
Synchronous EGFR mutations	N 24 (%)
Sensitising mutations	
L858R	4 (34%)
Exon 19 del	2 (16%)
G719X	4 (34%)
G719C	1 (8%)
G719S	1 (8%)
Resistance mutations	
T790M	6 (50%)
S768I	6 (50%)

Table 2 First-line treatment in patients with *EGFR co-occurring* mutations ($n = 8$)

	No. of patients	Disease control rate	Median duration of response (months)
EGFR-directed therapy (Erlotinib)	5 (63%)	60%	6(4–54)
Cytotoxic chemotherapy	3 (37%)	67%	11(10–12)

These mutations can develop on therapy and serve as a mechanism of acquired resistance to TKI therapy. Less commonly, they can be detected concurrently with the sensitising mutation at the time of diagnosis (reference Yu et al. *Annals Oncology 2014* and Zhu et al. *Target Oncol 2017*).

A PubMed review was undertaken of studies published between 2010 and 2016 that evaluated outcomes for synchronous primary sensitising and resistance EGFR mutations. In total three papers, Yu et al. (*Annals Onc*, 2014), Su et al. (*JCO*, 2012), and Yang et al. (*Lancet Oncol*, 2015) identified 48 patients with synchronous primary sensitising and resistance EGFR mutations who received targeted therapy (erlotinib or gefitinib) with response rates of between 8–14%, median PFS 1.5–8.2 months, and median OS 15–21 months (Table 1). These patients were mostly of Asian ethnicity.

We previously published data on a large cohort of Irish NSCLC patients demonstrating an 8% *EGFR* mutation rate [6]. Here, we examine the incidence, treatment, and clinical outcomes for patients with synchronous primary sensitising and resistance EGFR mutations in a large cohort of Irish NSCLC patients.

Methods

We conducted a retrospective review of all lung cancer patients attending HSE South who had specimens sent for EGFR analysis. Tumour samples were tested for EGFR mutations using both the Cobas EGFR Mutation Test v2 (Roche Pharmaceuticals) and next-generation sequencing.

With the cobas test, formalin-fixed and paraffin-embedded tumour samples are analysed using polymerase chain reaction (PCR) for 42 alterations in exons 18, 19, 20, and 21 of the *EGFR* gene.

A reference pathology laboratory at St. James Hospital was also interrogated to identify all NSCLC patients with co-occurring *EGFR* resistance and sensitising mutations at diagnosis who were diagnosed between December 2009 and October 2015.

In tumours harbouring de novo *EGFR* sensitising and resistance mutations, baseline demographic, clinical and tumour-related characteristics were recorded. Treatments

Table 3 Response to erlotinib in patients with tumours containing baseline EGFR T790M mutations

Patient I.D.	Age	Gender	Baseline PS	EGFR Sensitising mutation	EGFR Resistance mutation	EGFR TKI Line	Best Response	PFS on TKI(months)	Median OS(months)
1	65	F	0	L858R	T790 M	2	PD	1	15
2	63	M	1	Exon 19	T790 M	2	SD	23	34
4	63	F	0	Exon 19	T790 M	1	SD	54	96+
8	59	F	2	G719X	T790 M	1	PD	1	3

Table 4 Response to erlotinib in patients with tumour-containing baseline EGFR S768I mutations

Patient I.D.	Age	Gender	Baseline PS	EGFR sensitising mutation	EGFR resistance mutation	EGFR TKI line	Best response	PFS on TKI (months)	Median OS (months)
3	76	F	1	G719X	S768I	1	PR ongoing	28+	30+
5	66	F	1	G719C	S768I	1	PR ongoing	6+	6+
6	67	F	1	G719S	S768I	1	SD	4	5
7	67	F	0	L858R	S768I	–			16

administered, data on response to treatment, and overall survival was obtained. Response to treatment was assessed radiologically. Data cutoff for follow-up was February 1, 2017.

Statistical analysis

All analyses were carried out by SPSS software. Demographic and clinical data were summarised as medians with ranges for continuous variables and categorical variables were expressed as the means of absolute and percentage numbers.

Results

Between December 2009 and February 2015, 334 tumour samples were tested for EGFR in our institution's laboratory. 4/334 (1%) of our cohort tested positive for de novo co-occurring EGFR sensitising and resistance mutations.

Twelve cases nationally were identified. Four (33%) were men and 8 (67%) were women. Median age at diagnosis was 65 years (range 52–79 years). One (8%) was stage I–II at diagnosis. One (8%) was stage III at diagnosis, and 10 (83%) were stage IV at diagnosis. All 12 (100%) were histologically adenocarcinoma subtypes. Follow-up was available on 8 patients. Four patients were reviewed at other institutions and follow-up data was unavailable.

The majority (68%) of the sensitising mutations occurred at L858R and G719X. Of the 8 patients on whom follow-up data was available, 50% of the resistance mutations were T790M and 50% were S768I (Table 1).

All eight patients received an EGFR TKI with an overall response rate of 25%, median PFS 24 months, and median OS 34 months. Five patients (63%) received erlotinib in the first-line setting with a 60% disease control rate (DCR) and a median duration of response of 6 months (range 4–45 months). Three (37%) received cytotoxic chemotherapy in the first-line setting with 67% DCR and a median duration of response of 11 months (range 10–12 months) (Table 2).

In patients with de novo EGFR T790M mutations, 50% (2/4) had stable disease with 1 patient having an ongoing response to erlotinib of over 96 months (Table 3). In patients with de novo EGFR S768I mutations who received erlotinib, 50% (2/4) have ongoing partial responses at 30 and 6 months respectively (Table 4).

Discussion

We present a cohort of 8 patients harbouring de novo sensitising and resistance mutations to EGFR TKIs who received treatment with erlotinib in Western population. To our knowledge, this is only the second report in the literature describing treatment outcomes for these patients in a Western population (reference Yu et al, *Annals Oncology, 2015*). Incidence of co-occurring EGFR mutations in our cohort of NSCLC is 1% on routine assays. Erlotinib appears to have activity in this cohort in both in the first- and second-line setting.

Consistent with previous studies, it appears that first-generation TKIs such as erlotinib, gefitinib, and icotinib may be the optimal choice of therapy for patients with complex mutations containing 19 del or L858R mutations [5].

Limitation of this study includes its retrospective design and small sample size numbers. EGFR mutations are heterogeneous and should be analysed separately.

Our study demonstrates the challenges of researching and treating low-incidence disease subtypes. International cooperation is required to continue to develop the field and further investigation is required to clarify differences in biological activity within this group. Real world data has important contributions to make and should be incorporated into research. It has the potential to identifying safety signals, provide quality control, direct practice guidelines and identify important biological connections.

Compliance with ethical standards

Conflict of interest This manuscript is in compliance with Committee on Publication Ethics and the authors have no conflict of interest to disclose.

References

1. Jemal A, Siegel R, Xu J et al (2010) Cancer statistics, 2010. CA Cancer J Clin 60:277–300 CrossRef, Medline
2. Lee CK, Brown C, Gralla RJ et al (2013) Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst 105:595
3. Zhou C, Wu YL, Chen G et al (2011) Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12:735
4. Moran T, Sequist LV (2012) Timing of epidermal growth factor receptor tyrosine kinase inhibitor therapy in patients with lung cancer with EGFR mutations. J Clin Oncol 30:3330
5. Zhang Y, Wang Z, Hao X, Hu X, Wang H, Wang Y, Ying J (2017) Clinical characteristics and response to tyrosine kinase inhibitors of patients with non-small cell lung cancer harboring uncommon epidermal growth factor receptor mutations. Chin J Cancer Res 29(1):18–24. https://doi.org/10.21147/j.issn.1000-9604.2017.01.03
6. Kelly D, Mc Sorley L, O'Shea E et al. (2017) A regional analysis of epidermal growth factor receptor (EGFR) mutated lung cancer for HSE South. Ir J Med Sci 9. https://doi.org/10.1007/s11845-017-15