Lung Cancer 115 (2018) 135–142

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

Uncommon mutations in epidermal growth factor receptor and response to first and second generation tyrosine kinase inhibitors: A case series and literature review

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ARTICLE INFO

Keywords:
Uncommon mutation
EGFR
Tyrosine kinase inhibitor
Response

ABSTRACT

Epidermal growth factor receptor (EGFR) is the most common driver gene involved in non small cell lung cancer (NSCLC) growth, being found in approximately 10–15% of Caucasian and 40% of Asian patients. A wide variety of pathogenic mutations, deletions, insertions and duplications have been described in EGFR exons 18–21. The presence of the most common among them (e.g. exon 21 L851R and exon 19 deletions) is associated to response to first and second generation EGFR tyrosine kinase inhibitors (TKIs), which have demonstrated clear superiority over chemotherapy in terms of both progression free survival (PFS) and overall survival (OS) in all treatment lines. However, scarcity of data exists in literature about the response of rarer EGFR alterations to first and second generation TKIs, most works consisting in sporadic case reports and small case series. In this review we aim to discuss the available evidence about this topic, in order to derive suggestions for clinical practice. Furthermore, we report seven cases of patients with lung tumors harboring uncommon EGFR mutations, treated in our Institution with first or second generation TKIs.

1. Introduction

Lung cancer is very common both in men and women, and it is the leading cause of cancer-related deaths worldwide [1]. As lung cancer diagnosis is frequently performed in advanced stages, most treatment strategies do not have curative intent and prognosis remains poor [2]. Recent advances in molecular characterization of lung cancer underlined the role of specific genes involved in cancer proliferation, especially in adenocarcinoma [3]. Epidermal growth factor receptor (EGFR) was the first driver gene to be discovered in non small cell lung cancer (NSCLC). In normal cells, the binding of epidermal growth factor (EGF) to its specific receptor induces cellular proliferation through RAS and PI3 K/AKT pathways. EGFR mutation induces constitutional activation of these intracellular routes, leading to uncontrolled cell growth, tissue invasion and metastatization [4]. The prevalence of EGFR mutations is about 10% in the Caucasian population and 40% in the Asiatic population. EGFR mutant NSCLC is more common among females and never-smokers or previous light-smokers. A strong association exists between EGFR driver mutations and adenocarcinoma histology, although rare cases of EGFR mutated squamous, mixed adeno-squamous and poorly differentiated lung cancers have been described [5]. Advanced NSCLC patients harboring activating EGFR mutations are known to derive a great benefit from EGFR tyrosine kinase inhibitors (TKIs) [6–10]. EGFR mutations can involve exons 18, 19, 20 and 21. In particular, exon 19 deletion of 15–18 base pairs accounts for more than 50% of cases, while exon 21 point mutation at the residue L858R represents about 30% of them [11,12]. While the efficacy of EGFR TKIs for the most common EGFR mutations is established, much less is known about rare mutations such as exon 20 insertions, L861Q, S768I, G719X and so on, as most of the data consist of single case reports or small case series [13–15]. In this work we will perform a literature review about prevalence and response to first and second generation TKIs of uncommon EGFR mutations, together with a descriptive analysis and a qualitative synthesis of data from clinical trials and case reports. Furthermore, we will present a case series of seven NSCLC patients harboring uncommon or complex EGFR mutations, treated in our Institution with a first or a second generation TKI.

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https://doi.org/10.1016/j.lungcan.2017.12.002
Received 26 October 2017; Received in revised form 27 November 2017; Accepted 3 December 2017

Table 1
Single patient analysis of response to first and second generation TKIs for different groups of EGFR mutations.

Mutations	N	TKI	BOR	RR	DCR
Exon 18					
G719any[a]	142	108 (E, G)	38 PR, 34 SD, 34 PD, 2 NA	35.2%	66.7%
E709-T710 deletions	6	4 (E, G)	1 SD, 3 PD	0.0%	25.0%
E709any[b]	5	3 (E, G)	2 SD, 1 PD	0.0%	66.7%
S720any	5	3 (E)	1 SD, 2 PD	0.0%	33.3%
Other point mutations[c]	23	17 (A, E, G)	2 PR, 4 SD, 10 PD, 1 NA	11.8%	35.3%
Exon 19					
V742any	3	3 (E, G)	2 PR, 1 SD	66.7%	100.0%
E746any	3	0	NA	NA	NA
Other point mutations	12	12 (A, E, G)	1 PR, 4 SD, 4 PD, 3 NA	8.3%	41.7%
Multiple codon insertions	4	1 (E)	1 PR	100.0%	100.0%
Exon 20					
S768I	20	15 (A, G, E)	4 PR, 6 SD, 5 PD	26.7%	66.7%
Multiple codon insertions from A767	17	9 (E, G)	5 SD, 4 PD	0.0%	55.6%
Multiple codon insertions from D770	9	4 (E, G)	1 PR, 1 SD, 2 PD	25.0%	50.0%
Multiple codon insertions from H773	8	4 (E, G)	2 SD, 2 PD	0.0%	50.0%
S768I + other exon 20 mutations	7	5 (E, G)	1 PR, 3 SD, 1 PD	20.0%	80.0%
De novo T790M	7	6 (E)	1 PR, 1 SD, 3 PD, 1 NA	16.7%	33.3%
Multiple codon insertions from S768	5	5 (E)	1 SD, 3 PD, 1 NA	0.0%	20.0%
V774any	4	4 (E, G)	1 PR, 3 PD	25.0%	25.0%
Multiple codon insertions from P772	3	2 (E, G)	2 PD	0.0%	0.0%
Other point mutations[d]	18	10 (E, G)	3 PR, 1 SD, 4 PD, 2 NA	30.0%	40.0%
Other single codon insertions	17	5 (E, G)	2 PR, 2 SD, 1 PD	40.0%	80.0%
Other multiple codon insertions	11	6 (A, E, G)	2 PR, 3 SD, 1 PD	33.3%	83.3%
Exon 21					
L861any[e]	79	70 (E, G)	27 PR, 24 SD, 19 PD	38.6%	72.9%
L858R + other exon 21 mutations	15	12 (E, G)	6 PR, 3 SD, 3 PD	50.0%	75.0%
V851any[f]	3	2 (E, G)	1 SD, 1 PD	0.0%	50.0%
H835any[g]	3	1 (E)	1 PR	100.0%	100.0%
A859any[h]	3	3 (E)	1 PR, 1 PD, 1 NA	33.3%	33.3%
V843any	3	2 (E)	2 PD	0.0%	0.0%
T854any[i]	3	3 (E, G)	1 SD, 2 PD	0.0%	33.3%
Other point mutations[j]	23	18 (E, G)	3 PR, 8 SD, 6 PD, 1 NA	16.7%	61.1%
Exon 18 + exon 19 complex mutations					
G719S + exon 19 deletions	1	0	NA	NA	NA
Exon 18 + exon 20 complex mutations					
G719any + S768I	19	18 (A, E, G)	9 PR, 7 SD, 1 PD, 1 NA	50.0%	88.9%
G719any + other exon 20 mutations	7	5 (G)	3 PR, 1 SD, 1 PD	60.0%	80.0%
Other complex mutations	1	1 (G)	1 PD	0.0%	0.0%
Exon 18 + exon 21 complex mutations					
G719any + L861Q	12	12 (E, G)	10 PR, 2 SD	83.3%	100.0%
E709any + L858R	13	13 (E, G)	5 PR, 7 SD, 1 PD	38.5%	92.3%
Other exon 18 mutations + L858R	2	1 (G)	1 PR	100.0%	100.0%
Exon 19 and exon 21 complex mutations					
Exon 19 deletions + L858R	4	2 (A, G)	2 PR	100.0%	100.0%
Exon 19 deletions + other exon 21 mutations	5	4 (G)	3 PR, 1 PD	75.0%	75.0%
Exon 19 point mutations + L858R	2	2 (G)	1 PR, 1 PD	50.0%	50.0%
Other complex mutations	1	1 (G)	1 PR	100.0%	100.0%
Exon 19 and exon 20 complex mutations					
Exon 19 deletions + T790M	4	3 (E, G)	2 PR, 1 PD	66.7%	66.7%
Exon 19 deletions + other exon 20 mutations	5	4 (E, G)	2 PR, 2 PD	50.0%	50.0%
Exon 20 and exon 21 complex mutations					
S768I + L858R	8	7 (A, E, G)	5 PR, 2 SD	71.4%	100.0%
Other exon 20 mutations + L858R	5	3 (G)	2 PR, 1 PD	66.7%	66.7%
T790 M + L858R[k]	5	3 (E)	2 PR, 1 SD	66.7%	100.0%

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