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Research Article

Epidermal Growth Factor Receptor Mutation and Lung Cancers, Current Evidence, a Brief Review

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Abstract

With the advances of target therapies, lung cancer patients overall survival had extended from previous 6 months to 2.5 years. Some patients even survived over 5 years more. It is important nowadays for general physicians have some knowledge of this topic. A brief review was conducted.

1. Does EGFR inhibitor more effective in mutant type than chemotherapy? How about subtype?
2. Does EGFR inhibitor more effective in wild type than chemotherapy?
3. Does EGFR inhibitor more effective in mutation type than the wild type? How about subtype?
4. Are there survival benefits of EGFR mutation type versus wild type?
5. EGFR resistant mechanism

Keywords: EGFR; Progression free survival; Overall-survival

Abbreviations

PFS: Progression Free Survival; OS: Overall-Survival

Epidemiology

EGFR mutations, *EGFR* gene copy number, and *EGFR* protein expression are three *EGFR*-related biomarkers [1-3]. *EGFR* mutations are present in the first four exons and about 90% of these mutations are either short in-frame deletions in exon 19, or point mutations that result in a substitution of arginine for leucine at amino acid 858 (L858R) [4-6].

Among severe Asian regions, *EGFR* mutation had been detected about 51.4% overall, but lowest in Indian 22.2% [7]. In Western population, around 15% (13.1-17.8%) *EGFR* mutation, 27.6% (465/1,683) *KRAS* mutations, and around 5% (4.4-7.1%) *ALK* rearrangements were identified [8,9]. Also, *EGFR* mutations and *ALK* rearrangement were mutually exclusive [8,9] but not with *KRAS*. In BR.21 trial, 3 patients had both *EGFR* and *KRAS* mutation [10]. *EGFR* mutation has only being reported 9.8% in Germany samples [11]. African Americans has been reported harboring *EGFR* mutation as low as 2% [12] but 21% mutation has been reported [13] in North African patients.

Among non-adenocarcinoma of the lung, 8.4% was associated with *EGFR* mutations [14].

EGFR mutant type

In recent studies, four published meta-analysis of *EGFR* mutant analysis had showed that TKIs treatment compared with chemotherapy has been associated with better PFS but not OS [15-18]. Only 1 of 4 paper used fixed effect model in meta-analysis (Table 1). Due to over all comparisons were not based on randomization and the extracted data used for this analysis could not be considered randomization. Also, most of the published articles provided the crossover rate only for the entire group of enrolled patients with out wild type or mutation subgroup data. The effect of treatment crossover on the out comes could not be examined in IPASS study, 64.3% *EGFR* mutation received *EGFR* TKIs post discontinuation [19]. As for OPTIMAL and CTONG-0802 trials, OS cannot be reached due to not mature yet. However, in their regimen, they used carboplatin instead of cisplatin [20] which has been long considered being a standard regimen.

Difference in exon 19, 21 mutation sequence has also been associated with different median PFS [21]. Exon 19 deletion has been associated with a better PFS than L858R mutation [19-20] but not OS [22]. Even among exon 19 deletion, deletions encompassing the entire amino acid string from L747 though E749 had better PFS but not OS than deletion at other sites [23]. Uncommon *EGFR* mutations were associated with poor OS than common mutation under TKI therapy [24,25]. Milella M et al., reported that those with higher *EGFR* gene copy number had a poorer PFS and OS than EGF Rmutation [26] after receiving TKI. On contrary, Lee Y et al., reported higher *EGFR* gene copy number and skin rash had been associated with better response rate and PFS compared with no amplification [27]. KRA Summation combined with *EGFR* mutations had been associated with a poor response [28].

On the other hand, there were around 10% (8.75%-13.9%)

Table 1: Baseline characteristics of the meta-analysis.

Study	End of search date	Published year	Treatment	Study selected meta-methods
Gao G et al (15)	1966 to June 10, 2011	2012	1st line	Randomized, random-effect
Xu C etl al (16)	Dec 31,2011	2012	1st line	Randomized, random-effect
Lee CK et al (17)	Jan 1,2004 to June6, 2012	2013	1st, 2nd and 3rd	Randomized, fixed-effect
Lee JK et al (18)	Dec 16,2013	2014	1st, 2nd and maintaneous	Randomized, Random effect

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Table 2: Progression free survival.

EGFRmut+	Placebo/N	HR (95% CI)
1st line		
Xu C etl al (16)	0/5	0.36 (0.31,0.43)
Lee CK et al (17)	1/12	0.43 (0.38,0.49)
Gao G et al (15)	0/6	0.37 (0.27,0.52)
Maintenance		
Lee CK et al (17)	3/3	0.34 (0.20,0.60)
2nd line		
Lee CK et al (17)	0/4	0.34(0.20,0.60)
EGFRmut-		
1st line		
Lee CK et al (17)	1/7	1.06 (0.94,1.19)
Lee JK et al (18)	0/4	1.53 (0.87,2.69)
Maintenance		
Lee CK et al (17)	3/3	0.81 (0.68,0.97)
2nd line		
Lee CK et al (17)	0/5	1.23 (1.05,1.46)
Lee JK et al (18)	0/6	1.34 (1.09,1.65)

Table 3: Overall survival.

EGFRmut+	Placebo/N	HR (95% CI)
1st line		
Xu C etl al (16)	0/3	1.00 (0.79,1.27)
Lee CK et al (17)	1/11	1.01 (0.87,1.18)
Gao G et al (15)	0/5	0.97 (0.77,1.15)
Maintenance		
Lee CK et al (17)	2/1	0.78(0.33,1.84)
2nd line		
Lee CK et al (17)	2/5	0.74 (0.45,1.19)
EGFRmut-		
1st line		
Lee CK et al (17)	1/6	1.00 (0.88,1.14)
Lee JK et al (18)	0/4	1.05 (0.91, 1.23)*
Maintenance		
Lee CK et al (17)	2/2	0.84 (0.69,1.04)
2nd line		
Lee CK et al (17)	2/5	0.93 (0.79,1.10)
Lee JK et al (18)	0/5	1.05 (0.93,1.19)*

*recalculated by author

discordance in *EGFR* mutation heterogeneity between the primary Chinese lung cancer tissue and the metastasis sites [29,30] and 15.7 discordance in Japan [31]. About a third of combined *EGFR*-mutated and wild-type were detected in a study of 85 patients [32]. So, direct sequencing or any methods might misclassify of *EGFR* mutation as WT.

The most common toxicity of TKIs is rash and the most serious toxicity is interstitial lung disease, which occurs in about 1% of patients and is fatal in 30% who develop this toxicity. In NCIC CTG BR19 Study of adjuvant setting of gefitinib, the most common serious adverse event was dyspneam (13% vs 7% of patients on gefitinib and placebo, respectively). Other serious adverse events were less frequent and occurred in ≤ 5% of patients, with the exception of infection and pain. Three of five deaths (60%) in the gefitinib arm were considered drug related.

EGFR wild type

As for wild type, TKI has been associated with better PFS in maintenance therapy but not 1st line or 2nd and 3rd line (Table 2). Wild type didn't have good response nor poor response to TKI in OS (Table 3).

Others TKIs

Other drugs including in phase III trial were icotinib. However, mutation status were not planed initially at randomization [33]. Afatinib has been shown to improved PFS in mutant type compared with Gemcitabine and cisplatin group (11.0 months vs 5.6 months) in LUX-Lung 6 study [34]. The OS result was still pending.

Survival benefit, mutation type better or wild type better

After brain metastasis, *EGFR* mutation didn't associated with better PFS or OS compared with wild type [35]. *EGFR* mutation has been associated with better PFS after treatment with TKI but not OS as well [33]. In stage IV lung cancer patients, *EGFR* mutations compared with wild type were more associated with lung, brain and bone metastasis. Bone metastasis was associated with poor OS [36]. Even more complicated, difference in transcriptional subgroups in *EGFR* mutated and *EGFR* wild types were associated with different OS [37].

Marks JL et al [38] tried to clarify the role of *EGFR* and *KRAS* mutation in prognosis but failed due to small sample size. Whether *EGFR* mutation is a poor prognosis factor for poor OS in the era of TKI remains largely unknown.

EGFR resistant mechanism

Mutant *EGFR* patients often develop acquired resistance to *EGFR* TKI after a median of 10 to 16 months [39].

Among 155 *EGFR*-mutant lung cancers with resistant to TKI, 63% had CGFR T790M mutation, whereas HER2 amplifications (13%, 3/24), MET amplification (5%, 4/75), small cell transformation (3%) occur less frequently [40]. Besides, LEE GK et al., [41] had reported a preexisting EGFR T790M mutation in 25% of patients with *EGFR*-mutant lung cancer in their 124 treatment-naive patients. Another reported around 5-11% of harboring *EGFR* T790M mutation prior to the therapy [42].

Cell line models resistant mechanisms were beyond the description of this paper. Interesting readers could review the following paper [43].

BR.21 trial had demonstrated better OS which later lead to the prove of TKI for 2nd and 3rd line of standard treatment. However, no OS were identified of TKI therapy with either wild type or mutant type *EGFR* [17]. Increased *EGFR* copy number by FISH has also been associated with a better OS and *KRAS* mutation seems associated with poor response of OS though the power was not enough [10]. Would it

possible that *EGFR* gene copy by FISH be the biomarker of better OS? Maybe higher *EGFR* gene copy number should be the issue.

In conclusion, TKIs therapy in *EGFR* mutation could lead to prolong PFS in 1st, 2nd and maintenance therapy but not OS. Further clarified the role of *EGFR* gene copy number and protein expression in the era of TKIs might be need.

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