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Marissa Viola
Lincoln Memorial University, DeBusk College of Osteopathic Medicine

Adam Kolatorowicz
Lincoln Memorial University, DeBusk College of Osteopathic Medicine

Jun Wang
Lincoln Memorial University, DeBusk College of Osteopathic Medicine, jun.wang@lmunet.edu

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Marissa Viola[1], Adam Kolatorowicz[2], Jun Wang[3]

[1]Osteopathic Medicine Student, DeBusk College of Osteopathic Medicine, Lincoln Memorial University, Harrogate, TN
[2]Department of Anatomy, DeBusk College of Osteopathic Medicine, Lincoln Memorial University, Knoxville, TN
[3]Department of Pathology, DeBusk College of Osteopathic Medicine, Lincoln Memorial University, Harrogate, TN

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Introduction

Lung cancer is a leading cause of death worldwide. Mutations of various genes have been identified in lung cancers, including epidermal growth factor receptor (EGFR), a receptor tyrosine kinase. Target therapy using tyrosine inhibitors (TKI) has improved clinical courses in most patient with mutant EGFR. However, resistance to these inhibitors has been noticed. Previous studies have shown that concurrent mutations of tumor driver genes other than EGFR, may affects responses to TKI treatments in these patients.

P53 is a tumor suppressor gene that can be activated by various cellular stress signals. Activated p53 is critical in maintaining cell homeostasis through its roles in DNA repair and programmed cell death[1,2] (Figure 1). Mutation of p53 has been seen in many malignant tumors, including lung adenocarcinomas[3].

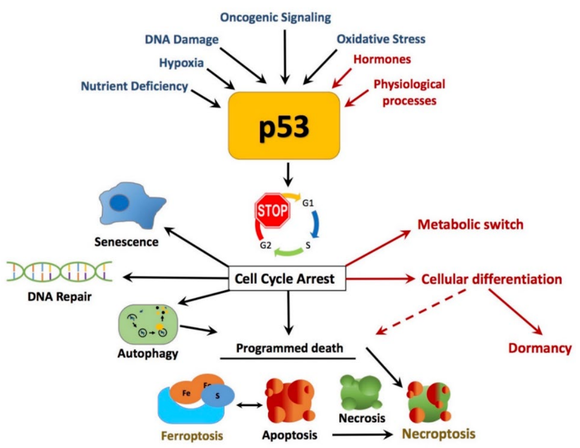

Figure 1. Signaling pathways of p53 in tumorigenesis, Moulder et al. 2018

In EGFR mutant lung cancer treated with first and second generation TKIs, concurrent p53 mutation appears to be associated with unsatisfactory response and/or shortened progress free survival (PFS)[4-8]. However, most of these observations revealed statistically insignificant results, partially due to small sample sizes, or non-standardized criteria. To better understand the association between concurrent mutation of p53 and resistance to TKIs, a meta-analysis was performed using published clinical trial observations.

Materials & Methods

Published studies for therapeutic outcomes of first and second generation TKI on EGFR mutant lung cancers are collected from PubMed following PRISMA guidelines. Various combinations of key words in title or abstract of *lung*, *EGFR*, *TKI*, *resistance*, *mutation* and *sequence* were used, with filters of clinical trial or randomized controlled trial. Abstracts of all the initial searching results were screened manually. Only original studies with status of p53 mutations, clinical outcomes of first and second generation TKIs, and progress free survival are included. Case reports, reviews, and studies using cultured cell lines were excluded. Full text of the remaining studies were reviewed.

Frequencies of p53 mutation were grouped either as baseline status in all patients receiving TKIs, regardless of clinical outcomes, or those with resistance. Odds ratios (OR) and hazard ratios (HR) were calculated using published findings from relevant studies. Standard errors for log HR were calculated using the formula (Upper95%-Lower95%)/2×1.96. Meta-analysis was conducted using RevMan 5.

Results

Included studies

Initial PubMed searching yielded 84 to 146 studies using different combination of key words described in Material and Methods. After reviewing abstracts/full text manuscripts, 31 studies were included for further analysis. Among these, 21 studies reported frequencies of p53 mutation, including 16 studies in baseline patient population and 11 in patients with TKI resistance. 10 studies reported frequencies of p53 mutation in both TKI sensitive and resistant patients. All patients involved in these studies have clinical stage III or IV disease.

Table 1. Frequencies of concurrent p53 mutation in EGFR mutant lung cancers receiving first and second generation TKIs.

Studies	Total pts tested	Mutant p53	%
Jin 2020	52	32	61.54
Canale 2017	123	37	30.08
Chang 2019	33	10	30.30
Cheng 2020	110	73	66.36
Deng 2019	24	9	37.50
Rachiglio 2019	133	23	17.29
Labbe 2017	105	43	40.95
Xu 2018	28	16	57.14
Kim 2018	75	43	57.33
Hou 2019	71	43	60.56
Yu 2018	200	119	59.50
Jakobsen 2018	21	10	47.62
Lim 2016	136	72	52.94
Tsui 2018	48	23	47.92
Jiang 2020	41	20	48.78
Vanderlaan 2017	20	10	50.00
Total	1220	583	$\bar{x}$ = 47.79

p53 mutation in EGFR mutant lung cancers

Concurrent p53 mutation is commonly seen in all EGFR mutant lung cancers, ranging from 17-66% (Table 1). Frequencies of concurrent p53 mutation in TKI resistant EGFR mutant lung cancer are similar, ranging from 12-87% (Table 2).

Table 2. Frequencies of concurrent p53 mutation in EGFR mutant lung cancers resistant to TKIs.

Studies	Pts with TKI resistance	Mutant p53	%
Canale 2017	21	11	52.38
Kim 2019	75	43	57.33
Yu 2018	136	89	65.44
Lee 2013	9	3	33.33
Jin 2016	53	27	50.94
Lim 2016	20	20	100.00
Otsubo 2019	24	9	37.50
Tsui 2018	16	7	43.75
Xu 2018	16	14	87.50
Fu 2021	50	19	38.00
Helman 2018	71	45	63.38
Total	491	287	$\bar{x}$ = 58.45

Various criteria in evaluating clinical outcomes

Resistance has been defined as PFS shorter than 4, 6 or 12 months, or grouped clinical responses as Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progress Disease (PD) (Table 3).

Table 3. Concurrent p53 mutation in TKI sensitive (S) and resistant (R) EGFR mutant lung cancers

Studies	Pts	p53+ (S:R)	p53− (S:R)	Outcome groups
Jin 2020	52	32 (16:16)	20 (10:10)	12 month
Canale 2017	123	37 (26:11)	86 (75:11)	Grouped response*
Kim 2019	75	43 (36:7)	32 (32:0)	Individual PFS**
Chen 2019	71	40 (21:19)	31 (20:11)	6 m vs 24 m
Jiang 2020	36	18 (17:1)	18 (17:1)	Grouped response*
Jakobsen 2018	23	10 (9:1)	13 (11:2)	Individual PFS
Labbe 2017	60	24 (23:1)	36 (34:2)	Grouped response*
Lim 2016	136	72 (52:20)	64 (64:0)	4 month
Xu 2018	28	16 (2:14)	12 (2:10)	6 month

* Sensitive responses include CR and PR; resistant responses include SD and PD
** PFSs of individual patients were extracted through tables or figures.

Probability of p53 mutation in association with resistance to first and second generation TKIs

Meta-analysis were performed using studies with available PFSs. When resistance was defined as PFS shorter than 6 months, an OR of 1.93 was yielded, with a 95% CI of [0.38, 9.85], suggesting that concurrent p53 mutation is associated with TKI resistance. However, this difference is not statistically significant (p=0.43) (Figure 2a). When resistance was defined as PFS shorter than 4 months, an odd ratio of 20.16 was yielded, with a 95% CI of [2.61, 155.75], suggesting that concurrent p53 mutation is associated with TKI resistance. This difference is statistically significant (p=0.004). Only two studies were included in this analysis, since in one study no patients had a PFS shorter than 4 months (Figure 2b).

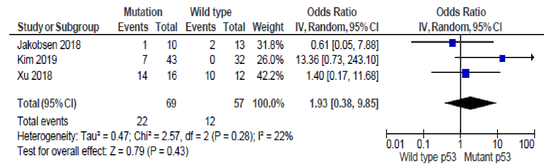

Figure 2a. Meta-analysis of three studies with resistance defined as PFS shorter than 6 months.

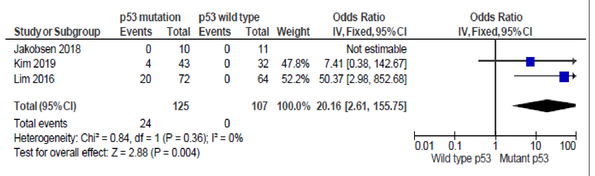

Figure 2b. Meta-analysis of three studies with resistance defined as PFS shorter than 4 months.

P53 mutation is associated with shortened PFSs in EGFR mutant lung cancer treated with 1st and 2nd generation TKIs

Seven studies with either reported HR or data that can be used to recalculate HR were included. A HR of 1.57 was yielded, with a 95% CI of [1.26, 5.53], suggesting that concurrent p53 mutation is associated with significantly shortened PFS (p<0.0001, Figure 3).

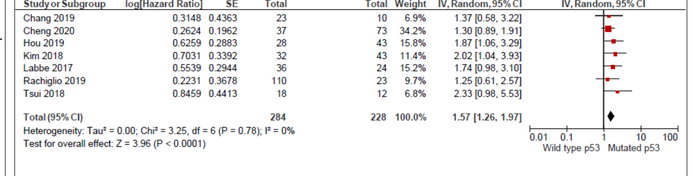

Figure 3. Meta-analysis of seven studies with available PFS.

Conclusion

1. Concurrent p53 mutation is commonly seen in EGFR mutant lung cancers.
2. Concurrent p53 mutation appears to be associated with TKI resistance in EGFR mutant lung cancers.
3. Concurrent p53 mutation is associated with shortened PFS in EGFR mutant lung cancer.
4. A more standardized definition of TKI resistance appears to be needed to further studies of molecular basis of TKI resistance in EGFR mutant lung cancers.

1. Vousden and Ryan. 2009. P53 and metabolism. Nat. Rev. Cancer. 9:691–700.
2. Moulder et al., 2018. The Roles of p53 in Mitochondrial Dynamics and Cancer Metabolism: The Pendulum between Survival and Death in Breast Cancer? Cancers. 10:189.
3. Kandoth et al., 2013. Mutational landscape and significance across 12 major cancer types. Nature. 502: 333–339.
4. Canale, et al., 2017. Impact of TP53 Mutations on Outcome in EGFR-Mutated Patients Treated with First-Line Tyrosine Kinase Inhibitors. Clin Cancer Res. 23:2195-2202.
5. Jin et al., 2018. Mutational profiling of non-small-cell lung cancer patients resistant to first-generation EGFR tyrosine kinase inhibitors using next generation sequencing. Oncotarget. 7:61755-61763.
6. Jakobsen et al, 2018. Concomitant driver mutations in advanced EGFR-mutated non-small-cell lung cancer and their impact on erlotinib treatment. Oncotarget. 9:26195-26208.
7. Xu et al., 2018. Short-Term Responders of Non-Small Cell Lung Cancer Patients to EGFR Tyrosine Kinase Inhibitors Display High Prevalence of TP53 Mutations and Primary Resistance Mechanisms. Transl Oncol.11:1364-1369.
8. Kim et al., 2019. Concurrent Genetic Alterations Predict the Progression to Target Therapy in EGFR-Mutated Advanced NSCLC. J Thorac Oncol. 14:193-202.
9. Jin et al. 2020. Distinct co-acquired alterations and genomic evolution during TKI treatment in non-small-cell lung cancer patients with or without acquired T790M mutation. Oncogene. 39:1846-1859.
10. Cheng et al., 2019. Concomitant Genetic Alterations are Associated with Worse Clinical Outcome in EGFR Mutant NSCLC Patients Treated with Tyrosine Kinase Inhibitors. Transl Oncol. 12:1425-1431.
11. Cheng et al., 2020. Comprehensive characterization and clinical impact of concomitant genomic alterations in EGFR-mutant NSCLCs treated with EGFR kinase inhibitors. Lung Cancer. 145:63-70.
12. Deng et al., 2019. Co-occurring genetic alterations predict distant metastasis and poor efficacy of first-line EGFR-TKIs in EGFR-mutant NSCLC. J Cancer Res Clin Oncol. 145:2613-2624.
13. Rachiglio et al., 2019. The Presence of Concomitant Mutations Affects the Activity of EGFR Tyrosine Kinase Inhibitors in EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC) Patients. Cancers (Basel). 11:341.
14. Labbe et al., 2017. Prognostic and predictive effects of TP53 co-mutation in patients with EGFR-mutated non-small cell lung cancer (NSCLC). Lung Cancer. 111:23-29.
15. Hou et al., 2019. Concurrent TP53 mutations predict poor outcomes of EGFR-TKI treatments in Chinese patients with advanced NSCLC. Cancer Manag Res. 11:5665-5675.
16. Yu et al., 2018. Concurrent Alterations in EGFR-Mutant Lung Cancers Associated with Resistance to EGFR Kinase Inhibitors and Characterization of MTOR as a Mediator of Resistance. Clin Cancer Res. 24:3108-3118.
17. Lim et al., 2016. Targeted sequencing identifies genetic alterations that confer primary resistance to EGFR tyrosine kinase inhibitor (Korean Lung Cancer Consortium). Oncotarget.7:36311-36320.
18. Tsui et al., 2018. Dynamics of multiple resistance mechanisms in plasma DNA during EGFR-targeted therapies in non-small cell lung cancer. EMBO Mol Med. 10:e7945.
19. Jiang et al., 2020. Predictive value of tumor genetic alteration profiling for chemotherapy and EGFR-TKI treatment in advanced NSCLC. Oncol Lett. 19:3859-3870.
20. VanderLaan et al., 2017. Mutations in TP53, PIK3CA, PTEN and other genes in EGFR mutated lung cancers: Correlation with clinical outcomes. Lung Cancer. 106:17-21.
21. Lee et al., Primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with non-small-cell lung cancer harboring TKI-sensitive EGFR mutations: an exploratory study. Ann Oncol. 24:2080-2087.
22. Otsubo et al., 2019. Genetic Profiling of Non-Small Cell Lung Cancer at Development of Resistance to First- or Second-Generation EGFR-TKIs by CAPP-Seq Analysis of Circulating Tumor DNA. Oncologist. 24:1022-1026.
23. Fu et al., 2021. Advanced NSCLC Patients With EGFR T790M Harboring TP53 R273C or KRAS G12V Cannot Benefit From Osimertinib Based on a Clinical Multicentre Study by Tissue and Liquid Biopsy. Front Oncol.11:621992.
24. Helman et al., 2018. eli-Free DNA Next-Generation Sequencing Prediction of Response and Resistance to Third-Generation EGFR Inhibitor. Clin Lung Cancer. 19:518-530.