Advances in Social Science, Education and Humanities Research, volume 653
Proceedings of the 2022 International Conference on Social Sciences and Humanities and Arts (SSHA 2022)

Genetic Mutations in Causing Non-small Cell Lung Cancers and Related Drugs' Efficiency

Zhiyou Ye[1,2]

[1] Zhejiang University
[2] University of Richmond
[*]Email: zhiyouye021699@163.com

ABSTRACT
Gene mutations play an important role in the occurrence and development of tumors. The research on tumors at the gene level is more and more in-depth, especially in the mechanism of tumorigenesis and antitumor therapy. Common oncogenes are essential for the survival of all cells (not only tumor cells). Therefore, drugs targeting these genes are important for helping patients overcome cancers and extending life expectancy. The mutation research of the whole gene family has become a powerful tool in tumor genomics, which has brought a lot of progress. Gene families can be determined by similar sequences and protein domains. Since genes of the same gene family usually have similar functions, we can find the signal pathways related to tumorigenesis by systematically sequencing these genes in the tumor genome. Currently, more and more research focuses on creating drugs targeting specific genes and some drugs performed well in helping patients overcome cancers, especially non-small cell lung cancer. As one of the most adverse cancers, non-small lung cancer accounts for about 80 percentage of all lung cancer and nearly 75 percentage of patients were diagnosed lately with low 5-year survival rate. The research focused on understanding drugs targeted genes associated with non-small cell lung cancer would help us to treat patients efficiently. Up to now, a lot of genes were confirmed in involving in regulating the tumorigenesis, especially the KRAS, EGFR, AlK, MET, etc.

Keywords: *Genes, mutations, therapy, drug, efficiency*

1. CURRENT FOUNDINGS

1.1KRAS Gene

As a member of RAS family, K-Ras gene is situated at the downstream of EGFR signaling pathway and is responsible for making a protein called K-Ras, which is a part of MAPK/ERK signaling pathway. The K-Ras protein can transmit extracellular signals (related to cell growth, growth and differentiation) to nucleus. Numerous drugs created were tested to be used to attack the mutated K-Ras gene specifically but failed, including Selumetinib, Trametinib, Cobimetinib. Since its discovery in 1983, researchers have been committed to developing new therapies for treating the mutation. Unfortunately, the protein structure of KRAS lacks the "deep pocket" structure that can be combined with traditional small molecule drugs, and it binds closely to GTP in the activated state, so it was once considered "not to be a drug". However, more than 30 percentage of non-small cell lung cancer patients own K-Ras mutation (G12C most common). Previously, lots of patients with K-Ras mutation received the treatment with PD-1/PD-L1 antibody or TCR-T cell therapy. The results posted by 2017 ASCO meeting revealed that, among 165 subjects, the effective rate of PD-1 antibody was as high as 33.3% for patients with both K-Ras mutation and TP53 mutation and the effective rate was 21.3% for patients with K-Ras mutation but not STK11/LKB or TP53 mutation. Besides, the T-cellular immune therapy was also frequently used in treating patients with K-Ras gene mutation. The researcher Steven A. Rosenberg, the originator of immune cell therapy, stated in the most authoritative New England Journal of Medicine: after receiving immune cell therapy, six of the seven metastases in the lung of a patient with KRAS mutant colorectal cancer shrank heavily and no serious adverse effects reported[1].

1.2 EGFR gene

Epidermal growth factor receptor is a member of the epidermal growth factor receptor (HER) family. As one

Copyright © 2022 The Authors. Published by Atlantis Press SARL.
This is an open access article distributed under the CC BY 4.0 license -http://creativecommons.org/licenses/by/4.0/.

of the most frequently mutated genes, EGFR is especially more common among Asian patients with non-small cell lung cancers compared with other ethnics. The most common mutation sites occur in exons 18,19,20 and 21. Specifically, there are two common mutations: deletion in exon 19 accounted for 45%, and the L858R point mutation in exon 21 accounted for 40-45%[2]. The first-generation drugs including Gefitibib, Erlotinib and Icotinib were used in treating exon 19 deletion and exon 21(L858R) mutation. They can bind reversibly to the ATP binding site of EGFR protein to inhibit its function, thus hindering growth and metastasis of tumor. However, since both normal cells and tumor cells contain EGFR protein, there would be a series of adverse reactions following treatment, including diarrhea and vomiting. The second-generation of targeted drugs including Afatinib and Dacomitinib can irreversibly bind to EGFR gene, which differentiate them from the first-generation drugs. Patients with mutation sites at G719X, l861Q and S768I shown relative positive response to Afatinib, but mutation at other sites did not show ideal response to Afatinib. In the process of clinical application, the efficacy did not indicate better response for the second-generation drugs compared with the first-generation drugs. Moreover, the second generation of targeted drugs show relatively greater side-effects compared with the first generation of drugs. Admittedly, the first generation and second generation drugs improved the patients' overall progression-free survivial (PFS) and objective response rates(ORRs)[3]. More than 2/3 percentage of patients developed the drug resistance after treatment of 1-2 years and 50% ~ 60% of EGFR inhibitor resistance is related to T790M mutation[4]. Later, the third-generation drugs including Osimertinib and Avitinib focused on fixing the secondary resistance, especially T790M mutation. As one of the first lung cancer drugs targeting EGFR T790M mutation (including 18, 19 and 21 mutations) and EGFR-TKI acquired resistance (T790M) of non-small cell lung cancer, Ositinib shows impressive results with overall time(OS) of patients 38.6 months and longest free survival(PFS) 18.9 months published by 2019 ESMO (ESMO, 2019). Compared with PFS record of 10.2 month of first-generation drug, the third-generation drug Ositinib shows obvious advantage.

1.3 ALK gene

Anaplastic lymphoma kinase (ALK), known as ALK tyrosine kinase receptor or CD246, mainly causes non-small cell lung cancer in three ways, including rearrangement, overexpression, and fusion (common types for patients with NSCLC). The ALK fusion with EML4 mutation occurs in 1/3 of non-small cell lung cancer patients without EGFR or KRAS mutations. The EML4 and ALK genes are located on p21 and p23 of human chromosome 2, respectively. The inverted fusion of the two gene fragments can make the tissue express a new fusion protein EML4-ALK, which can lead to tumorigenesis. The ALK fusion mutation has strong exclusivity, which indicate that when it mutates, other driving genes often do not mutate. Current drugs in treating the ALK include the first generation drug Crizotinib, second-generation ALK-TKI Ceritinib,Alectinib, Brigatinib and third-generation ALK-TKI Loratinib. The Crizotinib is still the only first-line treatment for patients with ALK mutation in a lot of developing countries. Previous research based on 343 patients with ALK-positive nonsquamous NSCLC already confirmed that efficacy of first-line Crizotinib treatment was significantly better than standard platinum including chemotherapy (PFS 10.9 month vs 7 month, ORR 74 percentage vs 45 percentage)[5]. Besides, subjects taking Crizotinib could effectively reduce the symptom of lung cancer and improved the quality of life significantly compared subjects with chemotherapy. However, some patients taking Crizotinib would own drug resistant mutations including L1196M, G1269A, L1152R, C1156, S1206Y, C1156Y, F1174C, D1203N etc. The second generation Certinib, Alectinib and Brigatinib can be used to target mutations, especially the most frequeny mutations L1196 M and G1269A. The research based on 8 studies with 626 patients showed the ORR 70 percentage, disease control rate 88 percentage and PFS 9.3 month[6]. Besides, the phase III clinical study ascend-4 confirmed the efficacy of Ceretinib: the study showed that PFS was 16.6 months in Ceretinib group and 8.1 months in chemotherapy group[7]. The treatment of Ceretinib reduced the risk of progression and death hugely. As a third-generation ALK inhibitor, Laratinib's first-line effective rate is up to 90 % with intracranial effective rate 75%. The research revealed that, among 30 newly treated ALK positive patients who used Lorlatinib as the first line: 27 patients had significantly reduced tumors with the effective rate 90%, and total intracranial remission rate 75%[8]. Moreover, for 59 patients who already used Crizotinib or chemotherapy, Lorlatinib was used as a second-line or third-line drug and the effective rate was still as high as 69%, and the total intracranial remission rate was 68%[8].

1.4 MET gene

Among the common gene mutations in NSCLC, the MET gene is also one of the most abundant mutations. As one of the proto oncogene, the c-MET (ceullular-mesenchymal to epithelial transition factor) encodes transmembrane receptor of hepatocyte growth factor and owns the tyrosine kinase(TKS) activity. Activated c-MET together with hepatocyte growth factor (HGF) can regulate the proliferation, differentiation and invasion of various tissues and cells. The mutation of exon 14 MET gene and amplification of MET gene have a relatively high incidence in patients with non-small cell lung cancer. The drug previously being used in targeting c-MET was still Crizotinib, which are ATP Competitive

multi-target protein kinase inhibitor of MET/ALK/ROS, and Cabozantinib, which is also multi-target small molecule tyrosine kinase inhibitor including MET, ROS1, RET and AXL, etc. No drugs specifically targeting the MET mutation in exon 14 being reported until recently.

2. FUTURE DIRECTIONS

2.1 EGFR Gene

The first drug targeting EGFR 20 insertion (the third common mutation) Rybrevant(JNJ-6372) was approved by FDA recently to be used for treating patients clinically. As a novel EGFR-MET bispecific antibody, the Rybrevant TM binds extracellular to inhibit tumor growth and lead to tumor cell death. The overall remission rate(ORR) was 40 % and the median reaction time was 11.1 months among 81 patients with EGFR 20 insertion[9]. Up to January 2019, the experimental results indicated that 28% among the 88 patients with evaluable response had achieved partial remission (PR). The 47 patients among them were resistant after previous treatment with third-generation EGFR inhibitors, and 10 achieved partial remission. These included 4 patients with C797S mutation, 1 with CMET amplification and 5 patients without identifiable EGFR/CMET dependent resistance. Another promising drug targeting EGFR 20 insertion with high selectivity Mobocertinib(TAK-788) also showed impressive clinical results[10]. Subjects were divided into two groups: the platinum treated group (PPP cohort) and the extended cohort (exclusion), which include 114 and 96 patients, respectively. In the PPP cohort, the ORR was 26%, and the median duration of remission was 17.5 months with the median PFS 7.3 months. For the exclude cohort, ORR and median PFS were 23% and 7.3 months, respectively, without reaching the median remission duration[10]. The numerical differences could not deny the degree of clinical benefit obtained by the two assessments was similar.

As the fourth generation EGFR inhibitor, BLU-945 was the small molecule oral medicine developed by Bluepring Medicines. The recently published data showed that BLU-945 is highly sensitive to L858R/T790M, L858R/T790M/C797S, Del 19/T790M, Del 19/T790M/C797, moderately sensitive to L858R/C797S and del 19/C797S. The drug's lethality against these mutations is 1000-2000 times higher than first-generation or third-generation drugs on the market. Besides, BLU-945 100mg/kg twice a day can significantly reduce the Del19/T790M /C797S tumor[11].

Moreover, as one potential “first in class” HER3 targeted antibody coupled drug (ADC), Patritumab Deruxtecan can be used for treating patients who already received the third-generation TKI but also owning disease progression and drug-resistant EGFR mutation, can be effective in treating NSCLC EGFR mutation. The objective response rate (ORR) of 57 patients treated with Patritumab Deruxtecan (5.6 mg / kg) was 39%, the disease control rate was 72%, and the median progression free survival (PFS) was 8.2 months[12].

Besides, for patients with C797S/T790M mutation after treatment of Ositinib, one promising drug Eai045 may be used in the future. Together with Cetuximab which can block the antibody therapeutic agent of EGFR dimerization and make the kinase more sensitive to allosteric agent Eai045, the new drug Eai045 could be effective in helping currently resistant EGFR TKIs since mouse-drive model already showed positive results[13]. Also, TQB3804 is also one of the promising fourth generation of EGFR targeted drugs and preclinical studies already showed that the drug has strong activity against T790M/C797, L858R/T790M/C797 and L858R/T790M. Currently, the phase I study of TQB3804(NCT04128085) is being carried out and 30 subjects were selected for oral administration. Moreover, Roche’s CHUGAI reported the preclinical data of new fourth generation EGFG inhibitor CH7233163. The drug acts on EGFR-Del19, L858R and T790M in a non-covalent manner and has very weak inhibition on wild EGFR(ACCR 2020).

2.2 KRAS gene

New drugs including Adagrassib(MRTX849), Sotorasib(AMG510), JNJ-74699157 (ARS-3248), LY3499446, and BI 1701963 could be helpful for patients with K-Ras gene mutation. As an efficient and selective inhibitor, the MRTX849 (C32H35CLFN7O2) specifically interrupts the KRAS dependent signal transduction since it can covalently binds to cytosine 12[14]. The potency and high selectivity of the MRTX849 could benefit patients largely. The drug already demonstrated transmembrane potency in a variety of animal models with KRAS G12C mutation. Moreover, the selectivity of KRAS G12C mutant is more than 100 times higher than that of wide-type KRAS and other proteins. In the published phase I/II trial data code named krystal-1(NCT03785249), Adagrassib's research results attracted much attention since the reported disease control rate of this drug for patients with specific mutation of non-small cell lung cancer was as high as 96%. Among the 51 patients with KRAS G12C mutant non-small cell lung cancer who participated in the trial, the objective remission rate was as high as 45%, which indicated that nearly half of the patients reduced the tumor focus by more than 30% after receiving adagrasib (MRTX849) treatment, and there was no progression or spread(32 EORTC meeting). More importantly, Adagrassib (MRTX849) can penetrate the blood-brain barrier and is also effective in patients with brain metastasis.

Sotorasib (AMG 510) is one of the first small molecule inhibitors that successfully target K-Ras. AMG

510 is more likely to bind to GDP after covalent binding with cysteine generated by KRAS G12C mutation, which reduces the affinity between GTP and K-Ras. It prevents guanylate exchange factor from catalyzing GTP to replace GDP, and inhibits its cell proliferation activity. The clinical trial results show the efficacy of Sotorasib in the treatment of K-Ras mutant lung cancer. A total of 124 patients with non-small cell lung cancer carrying K-Ras G12C mutation who had undergone immunotherapy or chemotherapy. After Sotorasib treatment, the overall objective remission rate (ORR) was 36%, the complete remission rate (CR) was 2%, and the partial remission rate (PR) was 35%; the disease control rate (DCR) was 81%; the median remission duration (DOR) was 10 months, and 58% of patients had sustained remission longer than 6 months[15].

Although new drugs targeting K-Ras G12C and K-Ras G12D mutation already has been tested in clinical trials, no drugs reported treating mutations of G12V, G12A, G12S, G12R, G13D, G13C, although patients with those mutations represent relatively less ratios.

2.3 ALK gene

Compared with the previously approved previous three generations of ALK inhibitors, the fourth-generation drug TPX-0131 already showed effective preclinical data: the drug has lower IC50 values (IC50 less than 6.6) for Ll1198F, G1202R, G1269A and wild-type ALK than other TKIs, indicating the potential priority of the fourth generation ALK inhibitor TPX-0131 for these targets[16]. Besides, one new secondary generation drug CT-707 already began phase I clinical trial in Peking, and total 13 patients showed the ORR (objective remission rate) of 87.5 % and the median PFS 13 months. Another fourth-generation drug NUV-655 is also deceived our attention since it can solve Lorlatinib, especially tumors with G1202R mutation/compound mutation G1202R and 1198M compound mutation G1202R and G1269A. The drug would be carried out in clinical tests soon.

2.4 MET gene

Compared with the previously approved previous three generations of MET inhibitors, the fourth-generation exciting to notice that three drugs targeting exon 14 MET gene has been reported by ASCO 2020-Tepotinib, Capmatinib and Savolitinib. A total of 24 NSCLC patients with MET amplification were tested after taking Tepotinib. The ORR of the overall patients was 41.7%. Among them, the ORR of tepatinib first-line treatment MET amplification was as high as 71.4%, that of second-line treatment met amplification was 30%, and that of third-line treatment was 28.6% with median PFS 4.2 months and overall 9-month progression free survival rate 40 %(ASCO, 2021). The Capmatinib alleviated the condition of 68% of newly treated patients and 41% of treated patients(ASCO, 2021). The median time (PFS) of no progression or death was 9.69 months in newly treated patients and 5.42 months in treated patients. Capmatinib showed a long-lasting effect since the median duration of efficacy (DOR) was 11.14 months for newly treated patients and 9.72 months for treated patients. For phase II clinical research of Savolitinib, there were 49.2 percentage of patients showed evaluable efficacy (n=61) and the disease control rate was around 93.4 percentage for patients with evaluable efficiency. Both PFS and OS data are still not mature enough.

2.5 STAT3 gene

As a member of signal transducer and activator of transcription (STATs), the STAT3 gene is being confirmed by researchers that it can help overcome the resistance of gefitinib resistance, which can be a promising therapeutic target for lung cancer treatment[17][18]. Preventing the activation of STAT3 can lead to the resistance cells being sensitive to gefitinib. The new STAT3 inhibitor W2014-S is being to discovered to strongly deter the

proliferation and invasions of cancer cells by selectively inhibiting the activation of STAT3 gene but not influencing other kinases. However, the research is still in vivo, more clinical trials needed to be tested in order to confirm the efficiency of the drug for treating patients with EGFR-TKI resistance.

3. CONCLUSIONS

Although lots of drugs are being invented and many of them have been put into clinical use, side-effects of drugs including diarrhea, nausea and vomiting cannot be ignored. Future researches should also pay attention to alleviate the side-effects of drugs, which can largely benefit patients.

Besides, although many drugs being reported and tested in clinical trials, we should also realize the pressure of drug development for various targets since thousands and hundreds of new drugs were declared to be failed. However, generally, with more and more targeted genes being discovered, we should also believe that the results of extensive molecular testing of non-small cell lung cancer are becoming more and more accurate and valuable.

REFERENCES

[1] Eric Tran, P.F.R., Yong-Chen Lu, Todd D. Prickett, T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer. The New England Journal of Medicine, 2016.

[2] Bing Han, X.Z., Rong-xin Zhang, Wang-Fu Zang, Zhong-Yuan Chen, Huai-Dong Song, Mutations of

the epidermal growth factor receptor gene in NSCLC patients. PMC, 2011.

[3] Niki Karachaliou, M.F.-B., Jillian Wilhelmina Paulina Bracht, EGFR first- and second-generation TKIs—there is still place for them in EGFR-mutant NSCLC patients. 2019.

[4] D.Westover, J.Z., B.C.Cho, Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. ScienceDirect, 2018.

[5] Benjamin J. Solomon, T.M., Dong-Wan Kim, Yi-Long Wu, First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer List of authors. The New England Journal of Medicine, 2014.

[6] Junsheng Fan, Z.X., Xiaoli Zhang, Yuqing Chen, Ruolan Qian, The efficacy and safety of alectinib in the treatment of ALK+ NSCLC: a systematic review and meta-analysis. PMC, 2018.

[7] Jean-Charles Soria, D.S.W.T., Rita Chiari, Yi-Long Wu, First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. 2017.

[8] Benjamin J Solomon, B.B., Todd M Bauer, Enriqueta Felip, Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Pubmed, 2018.

[9] FDA, FDA Approves First Targeted Therapy for Subset of Non-Small Cell Lung Cancer. 2021.

[10] Suresh S. Ramalingam, C.Z., Tae Min Kim, Sang-We Kim, James Chih-Hsin Yang, Mobocertinib (TAK-788) in EGFR exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): Additional results from platinum-pretreated patients (pts) and EXCLAIM cohort of phase 1/2 study. Journal of Clinical Oncology, 2021.

[11] S.S. Schalm, T.D., S.M. Lim, C-W. Park, J. Hsieh1, BLU-945, a highly potent and selective 4th generation EGFR TKI for the treatment of EGFR T790M/C797S resistant NSCLC. Blueprint Medicines, 2020.

[12] Pasi A. Janne, C.S.B., Wu-Chou Su, Melissa Lynne Johnson, Hidetoshi Hayashi, Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC). Journal of Clinical Oncology, 2021.

[13] Yong Jia, C.-H.Y., Euyoung Park, Dalia Ercan, Overcoming EGFR T790M and C797S resistance with mutant-selective allosteric inhibitors. NCBI, 2016.

[14] Jill Hallin, L.D.E., Lauren Hargis, Andrew Calinisan, The KRASG12C Inhibitor, MRTX849, Provides Insight Toward Therapeutic Susceptibility of KRAS Mutant Cancers in Mouse Models and Patients. NCBI, 2019.

[15] Ferdinandos Skoulidis, B.T.L., Grace K. Dy, Sotorasib for Lung Cancers with KRAS p.G12C Mutation. The New England Journal of Medicine, 2021.

[16] Brion W. Murray, D.Z., Wei Deng, Xin Zhang, Jane Ung, Vivian Nguyen, Han Zhang, Maria Barrera, Ana Parra, Jessica Cowell, Dong J. Lee, Herve Aloysius and Evan Rogers, TPX-0131, a Potent CNS-penetrant, Next-generation Inhibitor of Wild-type ALK and ALK-resistant Mutations. AACR Journal, 2021.

[17] Qiyao Zheng, H.D., Jianshan Mo, Yi Zhang, A novel STAT3 inhibitor W2014-S regresses human non-small cell lung cancer xenografts and sensitizes EGFR-TKI acquired resistance. 2021.

[18] Zhe Liu, L.M., Yiming Sun, Targeting STAT3 signaling overcomes gefitinib resistance in non-small cell lung cancer. Nature, 2021.