PERSONALIZED MEDICINE FOR DIAGNOSIS AND TREATMENT OF NON-SMALL-CELL LUNG CANCER

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Lung cancer, the most common cause of cancer death worldwide, with most patients dying from distant metastases, has become increasingly complex in achieving effective treatment. In lung cancer, particularly in non-small-cell lung cancer (NSCLC), EGFR, ALK, RET, ROS1, BRAF, KRAS, NRAS, NTRK, PIK3CA, DDR2, MET, and ERBB2 have been reported as key oncogenic drivers, which have led to the development and application of targeted therapeutic drugs aimed at these dysfunctional genes. Personalized medicine based on these oncogenic drivers offers the greatest potential benefit in the diagnosis and treatment of NSCLC patients. In particular, personalized medicine is importantly recommended for the treatment of advanced NSCLC. Here, we briefly summarize the significant application of personalized medicine based on key oncogenic drivers for the diagnosis and treatment of NSCLC with targeted therapeutic drugs, both globally and Vietnam.

Keywords: Personalized medicine, targeted therapy, lung cancer, non-small-cell lung cancer (NSCLC), diagnosis, treatment.

INTRODUCTION

On Global, With 2,206,771 new cases and 1,796,144 deaths, lung cancer was the second most commonly diagnosed cancer and the leading cause of cancer-related deaths in 2020[1]. In Vietnam, during the same year, it was estimated that there were approximately 26,262 new cases and nearly 23,797 deaths from lung cancer1. Despite significant advances in both diagnostic methods and treatment over recent years, the 5-year survival rate remains at just 16%, primarily due to late-stage diagnosis, resulting in poor prognosis (1). Based on histopathological characteristics, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) accounted for 85% and 15% of all lung cancer cases, respectively.

Personalized medicine involves using individual genetic, proteomic, and environmental information to assist in the prevention, diagnosis, prognosis, and treatment of cancer. Therefore, personalized medicine strategies for lung cancer, particularly NSCLC, focus on specific molecular features of each patient's tumor to ensure accurate diagnosis and the most effective treatment plan for NSCLC. Notably, there has been a major shift in NSCLC treatment, from using a single drug for all patients to employing targeted therapies tailored to the molecular characteristics of each individual's tumor (Figure 1)[2,3]. In NSCLC, personalized medicine targeting molecular biomarkers such as EGFR, ALK, RET, ROS1, BRAF, KRAS, NRAS, NTRK, PIK3CA, MET, and ERBB2 has been identified as a key strategy for diagnosis and treatment for these patients. Thus, to further understand the vital role of personalized medicine in the diagnosis and treatment of NSCLC, this report provides an overview of current personalized medicine strategies used in the diagnosis and treatment of NSCLC patients.

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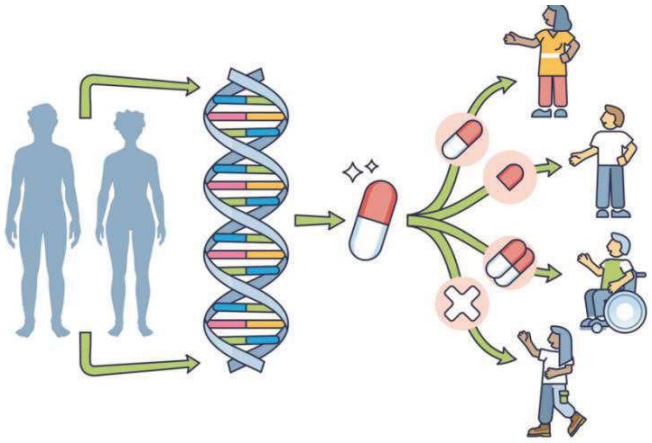

Figure 1. Personalized medicine in supporting disease treatment[3]

PERSONALIZED MEDICINE THERAPY AND MOLECULAR CHARACTERISTICS OF LUNG TUMORS

EGFR gene mutation

EGFR, a transmembrane receptor protein with tyrosine kinase activity, is known to play a crucial role in the pathogenesis of various cancers, including lung cancer. EGFR is one of the most attractive and widely studied targets for developing targeted therapies in cancer treatment. EGFR mutations, identified in 20 - 30% of NSCLC cases, particularly in adenocarcinomas, have been associated with potential benefits from targeted therapies, and several clinical trials have been conducted for NSCLC treatment4. EGFR mutations are especially more common in non-smokers and in Asian populations. The four main types of EGFR mutations include exon 19 deletion, exon 19 insertion, exon 20 insertion, and point mutations. The two most common EGFR mutations are exon 19 deletion (delE746-A750) and the point mutation (L858R) in exon 21, which together account for 90% of EGFR mutations in NSCLC. Other mutations include deletions or point mutations in exon 18 and exon 21, and less commonly, exon 20 insertions[4].

Additionally, most NSCLC patients with EGFR mutations will eventually develop resistance to first-generation EGFR inhibitors (Erlotinib, Gefitinib, and Icotinib) due to the emergence of a secondary T790M mutation in exon 20 of EGFR during treatment4,5. As a result, second-generation EGFR inhibitors (Afatinib and Dacomitinib) were developed to treat patients with secondary T790M mutations. However, NSCLC patients with secondary T790M mutations can also develop resistance to second-generation EGFR inhibitors over time. To address this, third-generation EGFR inhibitors (Osimertinib) were developed to treat NSCLC patients who became resistant to second-generation therapies (Afatinib and Dacomitinib) (Figure 2)[4,5].

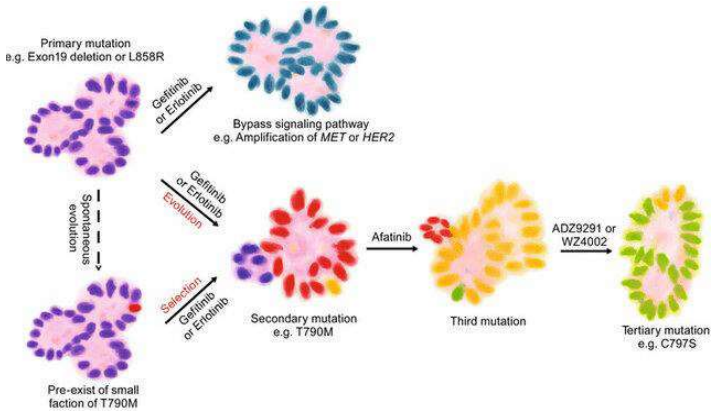

Figure 2. Molecular mechanisms of EGFR resistance in non-small cell lung cancer[5]

ALK gene fusions and mutations

ALK is a transmembrane receptor tyrosine kinase involved in various cancers, including lung cancer. The three oncogenic alterations in ALK are gene fusions, point mutations, and copy number amplifications. Among these, ALK gene fusions account for approximately 1 - 10% of non-small cell lung cancer (NSCLC) cases[4]. To date, 20 ALK gene fusion variants have been identified, with 11 of them (EML4-ALK, KIF5B-ALK, KLC1-ALK, HIP1-ALK, BIRC6-ALK, PRKAR1A-ALK, PPM1B-ALK, EIF2AK3-ALK, BCL11A-ALK, CEBPZ-ALK, and PICAM-ALK) contributing to the development and progression of NSCLC[6]. Notably, the EML4-ALK fusion is found in about 3 - 13% of NSCLC cases and is the most common variant. With the identification of ALK rearrangements in NSCLC, several targeted therapies have been developed: Crizotinib (a first-generation ALK and MET inhibitor), ceritinib and alectinib (second-generation ALK inhibitors), and Brigatinib and Lorlatinib (third-generation ALK inhibitors). These drugs are used effectively to treat NSCLC patients with ALK gene fusions. Another significant oncogenic alteration of ALK is point mutations. The mechanism of acquired resistance in NSCLC patients with ALK gene fusions treated with crizotinib has been attributed to secondary ALK mutations[6]. Secondary mutations in ALK that confer resistance to ALK-targeted therapies like crizotinib include 1151Tins, L1152R, C1156Y, F1174L, L1196M, L1198F, G1202R, S1206Y, G1269A, I1171T, D1203N, and V1180L. Consequently, to effectively treat patients with ALK gene fusions who have developed resistance to crizotinib due to secondary ALK mutations, second-generation ALK inhibitors (alectinib and ceritinib) are recommended. Furthermore, third-generation ALK inhibitors (lorlatinib and brigatinib) have been developed to address resistance in NSCLC patients previously treated with ceritinib and alectinib, especially those with acquired resistance due to the ALK mutation G1202R[6].

ROS1 gene fusion

ROS1, a receptor from the insulin receptor family with constitutive kinase activity, has been identified in NSCLC4. ROS1 gene fusion accounts for 1 - 2% of NSCLC cases and is associated with potential benefits from targeted therapies, with clinical trials being conducted for NSCLC treatment. To date, 14 variants of ROS1 gene fusion have been identified in NSCLC (CD74-ROS1, SDC4-ROS1, SLC34A2-ROS1, EZR-ROS1, TPM3-ROS1, LRIG3-ROS1, FIG-ROS1, KDELR2-ROS1, CCDC6-ROS1, MSN-ROS1, TMEM106B-ROS1, TPD52L1-ROS1, CLTC-ROS1, and LIMA-ROS1)[7]. Notably, the CD74-ROS1 variant occurs most frequently, and ROS1-targeted drugs (Crizotinib, Larotrectinib, and Entrectinib) have been used effectively to treat patients with ROS1 gene fusion in NSCLC[7].

RET gene fusion

RET, an oncogene, and RET gene fusion have been identified in approximately 1 - 2% of NSCLC cases[4] and are associated with potential benefits from targeted therapies, supported by clinical trials for NSCLC treatment. Five variants of RET gene fusion (KIF5B-RET, CCDC6-RET, NCOA4-RET, EPH5-RET, and PICALM-RET) have been identified in NSCLC[7]. Among these, the KIF5B-RET variant is the most common, representing 72% of cases, and RET-targeted drugs (cabozantinib and vandetanib) have been effectively used to treat patients with RET gene fusion in NSCLC[7].

BRAF gene mutation

BRAF, an intracellular serine/threonine kinase, activates the MAPK signaling pathway, regulating cell growth and proliferation. BRAF mutations account for 2 - 5% of NSCLC cases[4] and are associated with potential benefits from targeted therapies and clinical trials for NSCLC treatment. BRAF mutations are categorized into V600E (90%) and non-V600E subgroups (G469L and Y472C) and are typically identified in smokers or former smokers with NSCLC4. Specifically, all NSCLC cases with non-V600E BRAF mutations (G469L and Y472C)

have been found in heavy smokers. BRAF-targeted therapies (dabrafenib and vemurafenib) have been used to treat NSCLC patients harboring BRAF mutations.

KRAS gene mutation

KRAS, a gene in the RAS family, activates the RAF/MAPK and PI3K signaling pathways to control cell growth and proliferation. KRAS mutations are found in 32% of NSCLC cases4 and are associated with potential benefits from targeted therapies, supported by clinical trials for NSCLC treatment. The most common KRAS mutations are G12C (43%), G12V (18%), and G12D (11%). KRAS mutations are predominantly seen in NSCLC patients with adenocarcinoma, particularly among non-Asian smokers. Targeted therapies like Trametinib (a MEK1/2 inhibitor) have been used to treat patients with NSCLC harboring KRAS mutations. Notably, KRAS mutations are known to confer resistance to EGFR-targeted (erlotinib and gefitinib) and ALK-targeted (Crizotinib) therapies, making KRAS mutations a key factor in deciding against the use of these targeted treatments in NSCLC patients.

NRAS gene mutation

NRAS, a member of the RAS family and a GTPase related to KRAS, regulates cell growth, proliferation, and differentiation. NRAS mutations account for approximately 2 - 3% of NSCLC cases4 and are associated with potential benefits from targeted therapies and clinical trials for NSCLC treatment. NRAS mutations are frequently found in patients with a history of smoking. Trametinib (a MEK1/2 inhibitor) has been used to treat NSCLC patients with NRAS mutations.

NTRK gene fusion

NTRK, which includes three members NTRK1, NTRK2, and NTRK3 has been identified in about 1% of NSCLC cases4 and is associated with potential benefits from targeted therapies, with clinical trials supporting NSCLC treatment. ETV6-NTRK3 and TPM3-NTRK1 are the most common NTRK gene fusion variants identified in NSCLC. NTRK-targeted drugs (Larotrectinib and Entrectinib) have been used effectively to treat patients with NTRK gene fusion in NSCLC.

PI3KCA GENE MUTATION

PI3KCA, the catalytic subunit of the PI3K IA class, plays a critical role in regulating cell growth, survival, and motility. PI3KCA mutations are identified in approximately 5 - 6% of NSCLC patients4 and are associated with potential benefits from targeted therapies and clinical trials for NSCLC treatment. EGFR-targeted drugs (erlotinib and gefitinib) have been approved for treating NSCLC patients with PI3KCA mutations.

DDR2 gene mutation

DDR2, a tyrosine kinase receptor that binds to collagen types I and III, promotes cell proliferation, migration, and metastasis through epithelial-mesenchymal transition (EMT) mechanisms. DDR2 mutations are identified in approximately 4% of NSCLC cases[4] and are associated with potential benefits from targeted therapies and clinical trials for NSCLC treatment. SRC-targeted therapy Dasatinib has been used effectively in treating NSCLC patients with DDR2 mutations.

MET gene mutation

MET, a transmembrane tyrosine kinase receptor, plays a critical role in embryogenesis, tumor development, and metastasis. MET exon 14 skipping mutations have been identified in approximately 1 - 3% of NSCLC cases[4] and are associated with potential benefits from targeted therapies and clinical trials for NSCLC treatment. MET-targeted therapies (crizotinib, capmatinib, and glesatinib) have been used to treat patients with MET exon 14 skipping mutations in NSCLC.

ERBB2 gene mutation

ERBB2, a member of the ERBB family, activates downstream signaling pathways to promote oncogenesis in several cancers. ERBB2 copy number gain and ERBB2 mutations have been identified in 1 - 3% and 2 - 4% of NSCLC patients, respectively[4]. ERBB2 exon 20 insertion mutations

are associated with potential benefits from targeted therapies, with clinical trials supporting NSCLC treatment. ERBB2-targeted drugs (afatinib and neratinib) have been used to treat NSCLC patients with ERBB2 exon 20 insertion mutations.

CONCLUSIONS

Personalized medicine in the diagnosis and treatment of NSCLC patients with EGFR gene mutations, ALK gene fusions and mutations, ROS1 gene fusions, RET gene fusions, BRAF gene mutations, KRAS gene mutations, NRAS gene mutations, NTRK gene fusions, PIK3CA gene mutations, DDR2 gene mutations, MET gene mutations, and ERBB2 gene mutations has been tested in clinical trials and is indicated for NSCLC treatment. However, the rapid and accurate diagnosis of molecular target characteristics in NSCLC patients is crucial and necessary to support physicians in selecting effective treatment regimens. Therefore, Next-Generation Sequencing (NGS) is an optimal and important method for effectively implementing personalized medicine therapies in the treatment of each NSCLC patient based on their molecular characteristics. Notably, NGS is also the optimal method for identifying new molecular biomarkers for early diagnosis of lung cancer and for applying personalized medicine in the treatment of NSCLC patients.

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