·综　述·

ALK激酶域耐药突变的研究进展及未来应对策略

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［**摘要**］ 间变性淋巴瘤激酶（anaplastic lymphoma kinase，ALK）是非小细胞肺癌（non-small cell lung cancer，NSCLC）中常见的致癌驱动基因之一。酪氨酸激酶抑制剂（tyrosine kinase inhibitor，TKI）在*ALK*融合基因阳性的NSCLC患者中均取得了优异的治疗效果，然而患者最终会对TKI产生耐药性。获得性的分子生物学耐药，如ALK激酶域突变、*ALK*基因扩增和旁路异常激活等，是影响ALK$^+$ NSCLC靶向治疗效果的重要因素。获得性的ALK激酶域耐药突变现已成为关注重点。随着二代基因测序技术（next-generation sequencing，NGS）的不断进步及普及，ALK-TKI的耐药突变谱逐渐清晰，并且获得性耐药可能是动态变化的。首先，第一代、第二代TKI治疗失败后继发ALK激酶域耐药性突变以单点突变为主。约20%的患者在接受克唑替尼治疗失败后出现耐药突变，以L1196M、G1269A、C1156Y和F1174L为主。第二代TKI（包括阿来替尼、塞瑞替尼、布加替尼和恩沙替尼）耐药后点突变的发生率高达50%，且类型更丰富，例如G1202R/del、F1174C/V和I1171T/N/S等。相对于克唑替尼，第二代TKI对ALK激酶具有更高的抑制效果，可覆盖大部分的*ALK*耐药突变，但G1202R/del除外。研究发现，除G1202R是最常见的第二代TKI耐药性突变外，F1174C/L和I1171N/S/T分别是塞瑞替尼和阿来替尼的主要耐药突变，G1269A和E1210K是恩沙替尼的主要耐药突变位点。其次，第二代TKI耐药后*ALK*双重突变和“脱靶”比例显著增加。第三代TKI劳拉替尼耐药后几乎均为复合突变，并且耐药程度更高。现已发现I1171N-双重突变及G1202R-双重突变谱，其中，G1202R+L1196M双突变显示出对所有ALK-TKI的高度耐药。此外，序贯多代ALK-TKI治疗进展后，原有耐药位点发生变化，野生型的比列升高，耐药机制可能更为复杂。目前，在克唑替尼耐药后，序贯第二代/第三代TKI可抑制绝大部分耐药突变。而第二代TKI治疗进展后，可通过序贯其他第二代TKI或劳拉替尼达到抑瘤效果。对于顽固性的溶剂前沿区域突变，劳拉替尼对G1202R突变有显著的抑制效果，而对劳拉替尼耐药的L1198F突变及L1198F-双重突变对克唑替尼重新敏感。某些复合突变对第二代TKI敏感，如I1171N+L1196M和I1171N+G1269A突变，大部分复合耐药突变仍未发现有效的抑制剂。有新一代TPX-0131和NVL-655在临床前实验中以表现出优异的抑瘤效果，尤其是能够克服*ALK*复合耐药突变，但仍需要临床试验的验证。识别ALK-TKI的激酶域耐药突变谱，选择敏感且高效的TKI治疗是近年来的研究热点。本文聚焦于获得性ALK激酶域耐药机制，系统综述了*ALK*基因背景与激酶域耐药的关系和ALK-TKI激酶域耐药突变谱和治疗策略。同时，肿瘤进展后的重复活检对于识别ALK激酶域突变以及选择最有效的治疗策略至关重要。

［**关键词**］ 非小细胞肺癌；间变性淋巴瘤激酶；激酶域；突变；耐药

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Research progress of ALK kinase domain drug resistance mutation and its future countermeasures

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［**Abstract**］ Anaplastic lymphoma kinase (ALK) is one of the common oncogenic driver genes in non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitors (TKIs) have achieved excellent therapeutic effects in patients with *ALK* fusion positive NSCLC. However, patients will eventually develop resistance to TKIs. Acquired molecular drug resistance mechanisms, such as ALK kinase domain mutation, *ALK* gene amplification and abnormal activation of bypass, are important drug resistance mechanisms affecting the effect of targeted therapy for ALK$^+$ NSCLC. Acquired ALK kinase domain resistance mutations have become the focus of attention.

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With the deepening and popularization of next-generation sequencing (NGS), the drug resistance mutation spectrum of ALK TKI is becoming clearer, and acquired drug resistance may change dynamically. First, after the treatment failure of the first (G1)/second generation (G2) TKI, the secondary ALK kinase domain resistance mutation is mainly a single point mutation. About 20% of patients develop drug resistance mutations after failure of treatment with crizotinib, mainly L1196M, G1269A, C1156Y and F1174L. The incidence of point mutations following drug resistance to second-generation TKIs (including alectinib, ceritinib, brigatinib and ensartinib) is as high as 50%, and the types are more abundant, such as G1202R/del, F1174C/V and I1171T/N/S. In preclinical trials, compared with crizotinib, the G2 TKI has a higher inhibitory effect on ALK kinase and can cover most ALK resistance mutations, except G1202R/del. In addition to G1202R, F1174C/L and I1171N/S/T are the main drug-resistant mutations of ceritinib and alectinib respectively, and G1269A and E1210K are the main drug-resistant mutations of ensartinib. Secondly, the proportion of ALK double mutation and "off target" increase significantly following the resistance to the G2 TKIs. Following resistance to third generation (G3) TKI lorlatinib, almost all of them are compound mutations, and the degree of resistance is higher. I1171N double mutation and G1202R double mutation spectrum have been found. Among them, G1202R+L1196M double mutation shows high resistance to all ALK TKIs. In addition, after the progress of sequential multi-generation ALK TKI treatment, the original drug resistance sites change, the ratio of wild-type is increased, and the drug resistance mechanism may be more complex. At present, sequential G2/G3 TKIs can inhibit most drug-resistant mutations after crizotinib resistance. After the treatment progress of G2 TKI, the tumor inhibition effect can be achieved by sequential use of other G2 TKI or lorlatinib. For stubbern solvent frontier region mutation, lorlatinib has a significant inhibitory effect on G1202R mutation, while the lorlatinib resistant L1198F mutation and L1198F double mutation can be resensitized to crizotinib. Some compound mutations are sensitive to G2 TKIs, such as I1171N+L1196M and I1171N+G1269A mutations. Most compound drug-resistant mutations have not found effective inhibitors. The new generation TPX-0131 and NVL-655 show excellent antitumor effect in preclinical experiments, especially can overcome ALK compound drug resistance mutation, however, they still need to be verified by clinical trials. Identifying the kinase domain resistance mutation spectrum of ALK TKI and selecting sensitive and efficient TKIs treatment are the research hotspots in recent years. This paper focused on the mechanism of acquired ALK kinase domain resistance, and systematically summarized the relationship between *ALK* gene background and kinase domain resistance, ALK TKI kinase domain resistance mutation spectrum and treatment strategies. At the same time, repeated biopsy after tumor progression is very important for identifying ALK kinase domain mutations and selecting the most effective treatment strategy.

［**Key words**］Non-small cell lung cancer; Anaplastic lymphoma kinase; Kinase domain; Mutation; Drug resistance

间变性淋巴瘤激酶（anaplastic lymphoma kinase，ALK）是非小细胞肺癌（non-small cell lung cancer，NSCLC）中常见的致癌驱动基因，发生率约为5%，常见于无吸烟史、女性和年轻（中位确诊年龄为51岁）患者中[1-2]。目前，第三代ALK酪氨酸激酶抑制剂（tyrosine kinase inhibitors，TKI）（包括克唑替尼、塞瑞替尼、阿来替尼、布加替尼、恩沙替尼和劳拉替尼）在*ALK*融合基因阳性的NSCLC患者中均取得了优异的治疗效果。近年来的研究数据表明，TKI序贯治疗能极大程度地延长患者的生存期，*ALK*基因突变也因此有“钻石突变”美誉[3-4]。尽管靶向治疗疗效显著，患者最终会对靶向治疗产生获得性耐药[5]。*ALK*融合基因阳性NSCLC患者的耐药机制包括依赖ALK信号转导通路（*ALK*基因扩增和激酶域突变）、不依赖ALK信号转导通路（旁路激活和组织类型转化）以及伴随基因（*EGFR*、*KRAS*和*TP*53等）改变。本文聚焦于ALK耐药突变谱探索后续治疗方案和应对策略。

1 *ALK*基因背景与耐药

*ALK*基因位于染色体2p23位点，正常状态下可编码受体酪氨酸激酶（receptor tyrosine kinase，RTK）。RTK包含三部分结构，即细胞外区（接受外界信号）、跨膜区及位于细胞内的功能结构域。*ALK*基因主要在胚胎时期表达（合成蛋白质），促进神经系统的发育，之后进入休眠状态[6]。*ALK*基因变异（包括融合突变、点突变和基因扩增）导致激酶域异常激活，出现病理性ALK信号，诱发体细胞增殖和凋亡抑制，常出现在间变性大细胞淋巴瘤（anaplastic large cell lymphoma，ALCL）、炎症性肌成纤维细胞瘤（inflammatory myofibroblastic tumor，IMT）及

NSCLC等恶性肿瘤[7-9]。在NSCLC中，*ALK*融合突变是最常见的变异类型，以棘皮动物微管相关蛋白样因子4（echinoderm microtubule associated protein like 4，EML4）-*ALK*融合为主，约占85%，其他伴侣分子包括KIF5B、HIP1、GCC2及PLB1等[10-13]。

*ALK*点突变和基因扩增是导致NSCLC对ALK-TKI耐药的重要机制。所有接受TKI治疗的患者在耐药后都能发现*ALK*基因扩增[14-15]。点突变在初治患者中并不常见[16]，绝大多数都在癌细胞对TKI耐药的情况下出现[14]。*ALK*基因的常见突变位点于RTK细胞内激酶结构域，突变后导致相应部位氨基酸改变，蛋白质构象变化，形成空间位阻，干扰TKI与靶点的结合，导致获得性耐药[14，17]。

由于肿瘤发展的异质性，*ALK*基因突变位点和类型丰富而复杂[14，18-19]。首先，第一/二代TKI治疗失败后*ALK*基因的耐药变异以单点突变为主。约20%的患者在接受第一代TKI治疗进展后出现耐药突变，以L1196M、G1269A、C1156Y和F1174L为主；第二代TKI耐药后点突变的发生率更高（＞50%），类型更丰富，例如G1202R/del、F1174C/V和I1171T/N/S等[14，18，20]。其次，第二代TKI耐药后ALK双重突变和“脱靶”比例显著增加[14，21]。第三代TKI耐药后几乎均为复合突变，并且耐药程度更高，如G1202R+L1196M[22]。多代ALK-TKI治疗进展后，原有耐药位点发生变化，野生型的比列升高，耐药机制可能更为复杂[18]。

1.1 变异体与耐药突变

*EML4-ALK*变异体是影响获得性耐药的重要因素。已有研究[23-24]发现，V3变异体发生继发性耐药突变的概率高于V1、V2，突变类型及复合程度相对耐药性更高、更独特，如在V3中常见的*ALK*突变是C1156Y、F1174C/V、G1269A、I1171T、L1152R/V和G1202R，而L1196M突变在V1变异体中更常见。尤其，G1202R在V3变异体的发生率较V1变异体高（32% *vs* 0%，$P=0.001$）[23]，对G1/G2 ALK-TKI呈现普遍的高度耐药性，只有劳拉替尼对其效果明显[18，22]。

1.2 共存突变与耐药突变

在*ALK*融合基因阳性的NSCLC患者中，最常见的伴随突变是肿瘤蛋白P53（tumor protein P53，TP53）基因突变（＞20%）[25-27]。基线时具有*TP*53突变（*TP*53-mutant，*TP*53-MUT）患者的中位总生存期（median overall survival，mOS）显著劣于*TP*53野生型肿瘤（*TP*53-wild type，*TP*53-WT）的患者（44个月 *vs* 62个月，$P=0.018$）[28]。*TP*53共突变患者的突变负荷（tumor mutation burden，TMB）明显高于野生型患者（7.07±1.25 *vs* 3.20±0.33，$P=0.003$），且耐药突变的发生率也高于*TP*53野生型患者，表明*TP*53突变可能导致其肿瘤抑制功能受损，影响基因组稳定性，促进基因进化，最终诱发耐药突变[29]。

2 ALK-TKI获得性ALK激酶域耐药机制和治疗策略

*ALK*基因激酶结构域由较小的N瓣和较大的C瓣构成，通过“铰链区”链接[30]。ATP 结合位点位于N瓣和C瓣之间，核苷酸定位环（P 环）的下方。ALK-TKI通过与 ALK激酶结构域的ATP结合位点竞争性结合来达到抗肿瘤疗效[30]。ALK激酶域突变可分为5个热点区域：① ATP结合域（ATP-binding pocket）；② 核糖体结合口袋区域（ribose binding pocket）；③ α-C螺旋的N段或C段（N/C-terminal to the αC-helix）；④ 激酶铰链区（solvent front）；⑤ DFG基序（Asp-Phe-Gly）[17]。常见的具有较强耐药性突变位点是“门控”的 L1196、溶剂前沿的G1202和L1198以及DFG 基序附近的 G1269等[31]。

2.1 克唑替尼耐药谱

研究[14-15]发现，克唑替尼（crizotinib）治疗失败后，30%～45%的患者经克唑替尼治疗后会发生ALK激酶区基因突变和基因扩增。2010年，Chio等[31]首次发现L1196M、C1156Y两种突变，并且确认是克唑替尼的耐药机制。*ALK*-1196基因位于ATP结合域的底部，属“门控”关键位置，突变后形成空间位阻，影响药物与靶点结合，是克唑替尼治疗出现进展后常见的耐药突

变之一[31]。体外实验通过构建克唑替尼耐药细胞系时发现，耐药细胞不仅有获得性L1196M突变，还有*EML*4-*ALK*基因的拷贝数增加，提示获得性耐药可能是个动态过程，涉及基因扩增和点突变[15]。随着NGS研究不断深入，ALK-TKI的耐药突变谱逐渐清晰，L1152R/P、F1174L/V、G1269S、D1203N、I1171T、S1206Y及1151Tins等耐药性突变被陆续发现（表1）。

表1 既往报道中的ALK激酶域耐药突变谱

Tab. 1 Previously reported drug resistant mutations spectrum in ALK kinase domain

Mutation	Site	Resistance	Partner	Referance
G1123S	ATP-binding pocket	Crizotinib, ceritinib	EML4-ALK	[32]
G1128A	ATP-binding pocket	Crizotinib	EML4-ALK	[33]
T1151K/M	N-terminal to the α C-helix	Crizotinib, ceritinib	EML4-ALK	[34]
1151Tins	N-terminal to the α C-helix	Crizotinib, ceritinib, alectinib	EML4-ALK	[35-36]
L1152R/P	N-terminal to the α C-helix	Crizotinib, ceritinib	EML4-ALK	[37-38]
C1156Y	N-terminal to the α C-helix	Crizotinib, ceritinib	EML4-ALK	[17, 31, 39-40]
I1171T/N/S	C-terminal to the α C-helix	Crizotinib, alectinib, brigatinib	EML4-ALK	[22, 41-42]
F1174L	C-terminal to the α C-helix	Crizotinib, ceritinib	RANBP2-ALK	[17, 40, 43]
F1174V	C-terminal to the α C-helix	Crizotinib, ceritinib	EML4-ALK	[22, 40, 44]
F1174C	C-terminal to the α C-helix	Crizotinib, ceritinib	EML4-ALK	[40, 44]
F1174I	C-terminal to the α C-helix	Crizotinib, alectinib	EML4-ALK	[22]
V1180L	Gatekeeper mutation	Crizotinib, alectinib	EML4-ALK	[45-46]
L1196M	Gatekeeper mutation	Crizotinib, alectinib	EML4-ALK	[17, 22, 31, 39]
L1196Q	Gatekeeper mutation	Crizotinib, alectinib	EML4-ALK	[22, 47]
L1198F	Solvent front	Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib	EML4-ALK	[22, 38, 48]
L1198P	Solvent front	Crizotinib	EML4-ALK	[43]
G1202R/del	Solvent front	Crizotinib, alectinib, ceritinib, brigatinib, ensartinib	EML4-ALK	[22, 29, 35, 40, 44]
D1203N	ATP-binding pocket	Crizotinib, ceritinib	EML4-ALK	[43]
S1206Y/R	Solvent front	Crizotinib	EML4-ALK	[17, 35]
E1210K	Ribose binding pocket	Crizotinib, ensartinib	EML4-ALK	[27, 29]
F1245C	Asp-Phe-Gly motif	Crizotinib	EML4-ALK	[49]
L1256F	ATP-binding pocket	Crizotinib, lorlatinib	EML4-ALK	[22]
I1268L	Asp-Phe-Gly motif	Crizotinib	EML4-ALK	[22]
G1269A	Asp-Phe-Gly motif	Crizotinib, ensartinib	EML4-ALK	[39]
G1269S	Asp-Phe-Gly motif	Crizotinib	EML4-ALK	[17, 43]
R1275Q	α AL-helix	Crizotinib, ceritinib	EML4-ALK	[50]

2.2 第二代ALK-TKI

在克唑替尼治疗失败后，超过70%的患者选择接受后代ALK-TKI进行治疗，继续延长生存期[5]。相对于克唑替尼，第二代ALK-TKI（塞瑞替尼、阿来替尼、布加替尼和恩沙替尼）对ALK激酶具有更低的半数最大抑制浓度（median inhibition concentration，IC_{50}），可覆盖大部分的ALK耐药突变（表2），并显示出更好的中枢神经系统（central nervous system，CNS）渗透性[25-40]（表2）。

表 2 ALK激酶域耐药突变对ALK-TKI的应答反应

Tab. 2 Response of drug resistant mutations in ALK kinase domain to ALK-TKI

Mutation	Crizotinib	Ceritinib	Alectinib	Brigatinib	Ensartinib	Lorlatinib
G1123S	R	R	S	S	S	S
T1151K/M	R	R	S	P	U	S
1151Tins	R	R	R	P	U	S
L1152R/P	R	R	P	S	S	S
C1156Y	R	R	S	S	S	S
I1171T/N/S	R	S	R	S	S	S
F1174L	R	R	S	S	S	S
F1174V	R	R	P	P	S	S
F1174C	R	R	S	S	U	S
F1174I	R	U	R	P	U	U
V1180L	R	S	R	S	P	S
L1196M	R	S	R	S	S	S
L1196Q	R	S	R	S	U	S
L1198F	S	R	R	R	R	R
G1202R/del	R	R	R	R	R	S
D1203N	R	R	S	P	U	S
S1206Y/R	R	S	S	S	U	S
E1210K	R	P	P	S	R	S
F1245C	R	S	U	S	U	U
L1256F	R	U	S	U	U	R
G1269A	R	S	S	S	R	S
R1275Q	R	R	S	U	U	U

R: Resistant; S: Sensitive; P: Possible; U: Uncertain.

塞瑞替尼（ceritinib）与ALK的结合位置是由铰链区、P环、α-C螺旋和激活环组成的ATP结合口袋，主要限制野生型和突变型复合物中P环的构象改变[30]。在ASCEND-4研究[51]中，一线塞瑞替尼的中位无进展生存期（median progression-free survival，mPFS）显著优于化疗（16.6个月 *vs* 10.6个月，$P<0.001$）；在没有基线CNS转移的患者中，塞瑞替尼的mPFS长达26.3个月。对比化疗，克唑替尼进展和1/2线化疗失败的患者仍然能从塞瑞替尼治疗中获益（客观缓解率，overall response rate，ORR 42.6% *vs* 6.0%），mPFS（5.4个月 *vs* 1.7个月）更长[52]。在临床前模型中，塞瑞替尼能有效地抑制克唑替尼常见的耐药性突变，如L1196M、

G1269A、I1171T及S1206Y等[30, 40]。而且L1196M和I1171T/N/S突变点是塞瑞替尼独特的治疗位点[41]， ALK F1245C突变也对塞瑞替尼非常敏感[49]。而C1156Y、1151Tins、L1152R/P、R1275Q、G1202R/del、F1174V/C/L、T1151K及G1123S等突变会影响塞瑞替尼的结合位点产生耐药[14, 32, 34, 40, 50]。其中，G1202R 和F1174C/L是塞瑞替尼治疗失败后的主要耐药突变位点[14, 53]。G1123S 、T1151K和F1174C突变可导致P环出现波动，影响塞瑞替尼和P环之间较强的相互作用，导致耐药性的产生[32, 34]。而D1203、C1156、R1275、L1198及L1152等突变位点主要是由于影响塞瑞替尼与ALK的结合环境，干扰靶点的结合从而导致耐药性。*ALK* T1151Sins 突变导致患者对塞瑞替尼、阿来替尼产生耐药性，对劳拉替尼敏感[36]。

阿来替尼（alectinib）是经优化溶剂相互作用以及调节ATP结合位点后的高效选择性TKI，与野生型ALK结合位点主要在铰链区、P环及附近结构[54]。在ALEX研究中，阿来替尼组的mPFS为34.8个月，显著优于克唑替尼组的10.9个月（HR＝0.43，P＜0.000 1），并且显著改善ORR [55]。阿来替尼目前已成为ALK^+晚期NSCLC患者的一线治疗优先选择。对于克唑替尼难治性患者，是否携带*ALK*耐药突变基因影响阿来替尼的治疗效果，不携带耐药突变的患者的mPFS（9.1个月 *vs* 5.6个月）和ORR（45% *vs* 35%）更好[46]。在体外实验中，阿来替尼对大部分常见耐药突变有较高活性，如C1156Y、F1174L、G1269A及D1203N等[22, 50]。而研究[14, 46]发现，阿来替尼治疗失败后最常见的突变是G1202R和I1171N/S/T。*ALK* G1202R/del/K突变会导致阿来替尼耐药性[22, 56-57]。由于L1198、V1180、I1171N和L1196位点突变会影响ATP结合入口和铰链区的构象变化，诱导阿来替尼与ALK之间的“锁扣”作用发生变化[48]。诸如两种“门控”突变V1180L、*ALK* L1196M/Q及I1171T/N/S突变，对阿来替尼和克唑替尼均会产生耐药，但对塞瑞替尼、布加替尼及劳拉替尼等后代抑制剂敏感[22, 42, 45-47, 58]

布加替尼（brigatinib）是ALK/EGFR双重抑制剂，对*ALK* L1196M突变和*EGFR* T790M突变高度敏感[59]。*ALTA*-1L研究[60]显示，布加替尼的mPFS优于克唑替尼（24.0个月 *vs* 11.0个月，P＜0.001）。在克唑替尼耐药后患者中，布加替尼的mPFS为16.7个月[61]。在塞瑞替尼、阿来替尼甚至经历多线治疗（至少2种ALK-TKI）中，布加替尼仍然能获得7个月的mPFS[62-64]，从而确立了布加替尼在一代或其他二代ALK-TKI进展后的治疗地位。在临床前模型中，布加替尼对于ALK^+和ALK^-细胞均有更强的抑制活性，对于其耐药突变谱均有更高的抑制效力，对G1202R突变有中度抑制能力[38]。尽管对G1202R有抑制活性，高达70%的患者在接受布加替尼治疗失败后检测到新发的G1202R突变[14]。临床研究显示，布加替尼确实对许多继发性*ALK*突变显示出抗肿瘤活性，包括 L1196M、F1174L/V、G1269A、I1171N、L1198F和 V1180L等，与临床前试验显示的广谱活性相似[64]。布加替尼主要通过氢键与ALK-K1150、L1196、L1198和E1210残基产生相互作用，能耐受ATP结合口袋中的任何单一突变，但G1202R除外[65]。由于G1202R突变的存在，导致患者对布加替尼和神经营养性酪氨酸激酶（neurotrophic tyrosine kinase，NTRK）抑制剂的反应较差。因此，G1202R突变可能会导致布加替尼原发性耐药[66]。此外，有研究[14]显示，S1206C也会导致布加替尼耐药。

恩沙替尼（ensartinib）已获批用于治疗克唑替尼治疗后进展的或不耐受的ALK阳性的局部晚期或转移性NSCLC患者。在TKI初治患者中，恩沙替尼的mPFS（25.8个月 *vs* 12.7 个月；P＜0.001）和12 个月CNS进展率（23.9% *vs* 4.2%；P＝0.001）均优于克唑替尼[67]。在克唑替尼难治性患者中，恩沙替尼的mPFS为9.6个月，颅内ORR可达70%[68]。无论有无ALK激酶域耐药突变，恩沙替尼都表现出相似的ORR，对F1174L/V、C1156Y、T1151、G1123S和L1198F突变敏感性较高，再进展患者中最常见的继发性耐药突变是G1269A、G1202R和E1210K，而G1269A对其他第二代抑制剂敏感， G1202R对劳

拉替尼的治疗效果最明确[27, 29, 68]。

2.3 第三代ALK−TKI

劳拉替尼（lorlatinib）是第三代ALK-TKI，拥有更高的CNS渗透性，且可更广泛有效地克服已知的耐药性突变（表2）。CROWN研究[69]显示，劳拉替尼12个月无进展生存率（78% *vs* 39%）和ORR（76% *vs* 58%）显著优于克唑替尼。在克唑替尼耐药的患者中，劳拉替尼的ORR为73%（95% CI：60%～84%），mPFS为11.1个月（95% CI：8.2 个月～未达到），而且无论是否存在可检测的*ALK*突变，患者的ORR是相似的[18]。在二代ALK-TKI耐药背景下，劳拉替尼的抗肿瘤反应在不同*ALK*基因激酶域位点突变状态下产生差异，基于组织检测的*ALK*基因突变阳性患者的ORR（69% *vs* 27%）和PFS （11.0个月 *vs* 5.4 个月）明显优于突变阴性患者[18]。因此，在曾接受过至少一种ALK-TKI的患者中，对肿瘤组织进行再次检测是很有必要的，*ALK*基因突变情况可能提示患者接受劳拉替尼的疗效及持久获益程度。

劳拉替尼对几乎所有已发现的耐药性突变有良好治疗效果，包括已知的高耐药性突变1151Tins、G1202R、I1171N和F1174L等（表2）。特别是对ALK-TKI普遍耐药的G1202R/del，劳拉替尼显示明显的抑制效果，ORR可达到57%，mPFS为8.2个月[18, 22]。而ALK L1256F会导致劳拉替尼耐药，但该位点对阿来替尼敏感性很高。此外，劳拉替尼耐药后发生的L1198F突变会重新对克唑替尼敏感[22]。既往研究[19]还发现，劳拉替尼进展后更容易出现双重或多重复合突变，某些复合突变对第一代/第二代TKI会重新敏感，如V1185L+L1196M复合突变，然而很多高度耐药性的复合突变依然得不到有效抑制，如G1202R+L1196M，这种复合突变是目前劳拉替尼程度最高的耐药突变（IC_{50}=1 000 nmol/L），对所有的ALK-TKI都具有抗性[19]。

3 Solvent–front区域突变及治疗对策

Solvent-front区域是ALK激酶域的溶剂前沿，由突变诱导的构象变化和ALK-TKI与结合口袋之间的快速解离过程导致耐药性[54]。第二代TKI治疗失败后的耐药突变更容易出现于Solvent-front区域，比如G1202R/del、D1203N及L1198F[18, 27]。*ALK* L1198F突变导致蛋白ATP结合位点的构象变化，导致ALK激酶域结合位点与克唑替尼和劳拉替尼之间的亲和力的变化，使得癌细胞对劳拉替尼耐药，而对克唑替尼再次敏感[70]。顽固性的溶剂前沿G1202R突变对一代/二代TKI保持普遍高水平耐药，是二代TKI治疗失败后最常见的耐药突变。这与克唑替尼的结合位点毗邻Arg-1202，塞瑞替尼、阿来替尼的结合位点位于铰链区相关[14, 53]。除了劳拉替尼能有效抑制[18, 22]，新型抑制剂ZX-29也能克服G1202R突变导致的耐药性[71]。针对溶剂前沿区域（G1202R）合成的嘧啶-2,4-二胺衍生物对部分耐药突变有抑制活性，“半游离尿素”基团（仅有1个-NH部分）对最常见的L1196M突变（IC_{50}=0.91 nmol/L）以及G1202R（IC_{50}=4.3 nmol/L）有显著的抗肿瘤效果[72]。优化“尾巴”吡啶酮基序列，得到的2-氨基吡啶衍生物对L1196M（IC_{50}=45 nmol/L）、G1202R（IC_{50}=22 nmol/L）和ROS1（2.3 nmol/L）也表现出令人满意的抗肿瘤活性[73]。这些研究表明某些ALK特定区域的化学衍生物将是克服临床ALK激酶域耐药突变的有效方法。

4 复合耐药突变和治疗对策

ALK-TKI的多次序贯治疗后出现的双重复合突变已逐渐被认知。第二代ALK-TKI耐药后已出现一定比例的双重突变。V1185L+L1196M双重突变对阿来替尼反应较差，但是V1185L、L1196M和复合突变均对塞瑞替尼敏感[22]。I1171T+E1210K复合突变在塞瑞替尼耐药后出现[21]。E1210K+D1203N和F1174C+D1203N复合突变赋予克唑替尼和第二代抑制剂耐药性，劳拉替尼可克服[14, 22]。而劳拉替尼治疗后更容易出现多重复合突变[19, 22]。

研究[19]显示，接受连续靶向治疗后，有35%的患者在劳拉替尼治疗失败后出现*ALK*复合突变。由于*ALK* G1202R突变是第二代ALK抑制剂耐药后最常见的激酶结构域突变，含G1202R的复合突变可能成为接受序贯第二代和第三代TKI后再次进展的患者中最常见

的靶向耐药机制[19]。Okada等[22]在劳拉替尼治疗失败后的患者中发现，存在I1171N-双重突变（I1171N＝L1198F、+L1196M、+T1151K、+C1156Y、+F1174I、+L1198H、+L1256F和+G1269A）及G1202R-双重突变（G1202R＝L1198F、+G1269A、+L1196M、+F1174C、+F1174L和S1206Y）。此外，还有I1171S+G1269A、C1156Y+G1269A和高水平耐药的L1196M+D1203N等复合耐药突变[20, 74-75]。

G1202R+G1269A对劳拉替尼、塞瑞替尼耐药，虽然对布加替尼中度敏感，但是由于G1202R顽固耐药，临床应用布加替尼的效果可能受限[14, 22]。布加替尼对I1171N复合突变（+L1198F、+L1196M、+L1256F和+G1269A）有抑制效果；塞瑞替尼可抑制I1171N+L1196M和+G1269A；阿来替尼可抑制I1171N+L1256F[22]。值得注意的是，由于克唑替尼对L1198F的敏感性较高[59]，对劳拉替尼耐药的L1198F突变可再次从克唑替尼治疗中获益，也能克服L1198F-复合突变，如I1171N/G1202R/C1156Y+L1198F突变[19, 22]。其他复合突变类型，如I1171S+G1269A、G1202R+S1206Y、L1196M+D1203N和C1156Y+G1269A，再次应用第二代TKI可能对肿瘤有抑制效果，如塞瑞替尼、布加替尼[20, 74-75]。此外，第三代FMS样酪氨酸激酶-3（FMS-like tyrosine kinase-3，FLT3）抑制剂吉尔替尼（gilteritinib）对于I1171T/N/S单突变及I1171N-双重突变（+L1198F、+L1256F、+L1196M及+F1174I）有显著的效果[76]。

第四代TKI（TPX-0131和NVL-655）表现出显著的“双突变活性”，并且具有更强的CNS渗透性和对野生型ALK的抑制能力[77-78]。除了对已知单发耐药突变的广谱活性，TPX-0131对L1198F+G1202R、L1198F+L1196M、L1198F+C1156Y、E1210K+S1206C、T1151I+L1152ins和G1202R+L1196M有抑制能力。然而，G1202R+G1269A和G1202R+G1269A+L1204V复合突变仍会导致TPX-0131耐药[78]。目前第四代TKI已进入临床试验阶段，有望突破复合耐药突变的瓶颈。

5 展望

目前，第三代ALK-TKI在*ALK*融合基因阳性的NSCLC患者中均取得了显著的治疗效果，然而，耐药所致靶向治疗失败不可避免。*ALK*激酶域突变是ALK-TKI的重要耐药机制之一，认识和探索ALK激酶域耐药突变的发生机制和优化未来应对策略是ALK+NSCLC治疗中亟待解决的问题。迄今为止，*ALK*激酶域耐药突变大多为是临床前试验、小样本检测和个案报道，缺乏大规模临床研究数据明确TKI治疗后耐药突变的发生机制和对后代TKI的应答反应。目前，在克唑替尼进展后有第二代或第三代TKI可供选择，而第二代TKI治疗出现疾病进展后，仅有劳拉替尼作为“最后手段”。新一代TPX-0131和NVL-655在临床前研究中以表现出优异的抑瘤效果，尤其是能够克服*ALK*复合耐药突变，但仍需要临床试验的验证。同时，考虑到肿瘤的时空异质性以及个体耐药机制差异，仍建议在ALK-TKI治疗出现疾病进展后再次检测（包括活检和基因检测），有助于识别难治性和重敏性*ALK*基因激酶域突变，明确TKI的耐药机制，开展更具针对性的基础和临床转化研究，确立更加精准有效的治疗策略。

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