基于“竞争性释放”肿瘤细胞演化现象探索逆转TKI靶向治疗耐药的新策略

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摘要 恶性肿瘤发生发展与致癌基因突变活化密切相关, 靶向活化的致癌基因可以有效遏制恶性肿瘤的进展。特异性酪氨酸激酶抑制剂(tyrosine kinase inhibitors, TKI)因其在部分致癌基因活化的恶性肿瘤中能显著抑制肿瘤生长而受到临床医生和患者的青睐; 然而随着TKI靶向药物的广泛应用, 实践发现, 绝大部分恶性肿瘤患者在使用TKI后迟早会出现TKI耐药, 最终导致治疗失败。因此, 逆转或者延缓TKI耐药已成为当前研究的热点。TKI耐药机制包括致癌基因内部的继发突变、其他基因扩增或信号通路激活, 以及病理类型转变等。近年来, 基于对肿瘤演进研究的认识, 提出了耐药细胞的“竞争性释放”新观点。该文将整理相关文献, 对TKI靶向治疗过程中出现的耐药细胞“竞争性释放”从而导致TKI耐药, 以及如何基于此现象探索逆转TKI耐药的策略及方法作一综述。

关键词 竞争性释放; 肿瘤; TKI; 耐药

New Strategies in Reversing Resistance to Tyrosine Kinase Inhibitors Based on Competitive Release Phenomenon of Cancer Cell Evolution Dynamics

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Abstract One of the major reasons for the carcinogenesis and progression of cancer was the mutation of oncogenes and overproduction or activation of according oncoproteins. TKI (tyrosine kinase inhibitor) targeting special oncoprotein can inhibit the growth of cancer cells, and thus is recommended as a frontline in cancer treatment by a series of guidelines. However, the phenomenon of resistance to TKI will eventually occurred in cancer cells. Therefore, reversing or delaying TKI resistance has become the hot topic for cancer therapeutics. The mechanisms of TKI resistance include secondary mutations within oncogenes, amplification or signaling pathway activation of other genes, or the transformation of pathology type. Recently, with the advance of evolution theory in cancer progression, the concept of “competitive release” leading to dominance clone of drug-resistant cells has been proposed. We herein sum the related references about TKI resistance due to the “competitive release” of defiance subclones during the TKI therapy, and also we elaborate recent data about how to delay or reverse TKI resistance emerging from this circumstance of “competitive release”.

Keywords competitive release; tumor; TKI; resistance

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恶性肿瘤发生率日益增高, 已成为危害人类健康的主要杀手之一[1], 其中原癌基因突变引起细胞内相应激酶的组成性激活是导致细胞恶性转化的最主要原因[2-5]。研究报道, 在胃肠道间质瘤(gastrointestinal stromal tumors, GIST)患者中, 85%~90%存在c-kit或血小板源性生长因子受体α多肽(platelet-derived growth factor receptor alpha, *PDGFRA*)基因突变[6-8]; 在恶性黑色素瘤(malignant melanoma, MM)患者中, 约50%存在*BRAF*突变[9-10]; 在大约50%亚裔非鳞非小细胞肺癌(non small-cell lung cancer, NSCLC)患者中存在特有的表皮生长因子受体(epidermal growth factor receptor, *EGFR*)基因突变[3-4,11]。进一步研究表明, 上述原癌基因突变, 引起癌蛋白高表达活化, 可直接导致肿瘤细胞的异常增殖、侵袭转移等恶性表型; 而特异性靶向上述癌基因使其相应蛋白非活性化可有效抑制肿瘤细胞的生长增殖, 阻遏其侵袭转移。因此, 上述具有直接导致肿瘤细胞恶性表型的癌基因被称为“驱动基因”[12-14]。

大量临床试验结果表明, 与传统化疗相比, 靶向特定的驱动基因可显著提高晚期恶性肿瘤患者的客观缓解率(objective response rate, ORR), 延长患者的无进展生存期(progression-free survival, PFS)及总生存期(overall survival, OS)[12-17]。因此, 基于上述研究, 各大指南已推荐将特异性靶向药物作为具有相应敏感基因突变的晚期恶性肿瘤患者的一线选择方案。

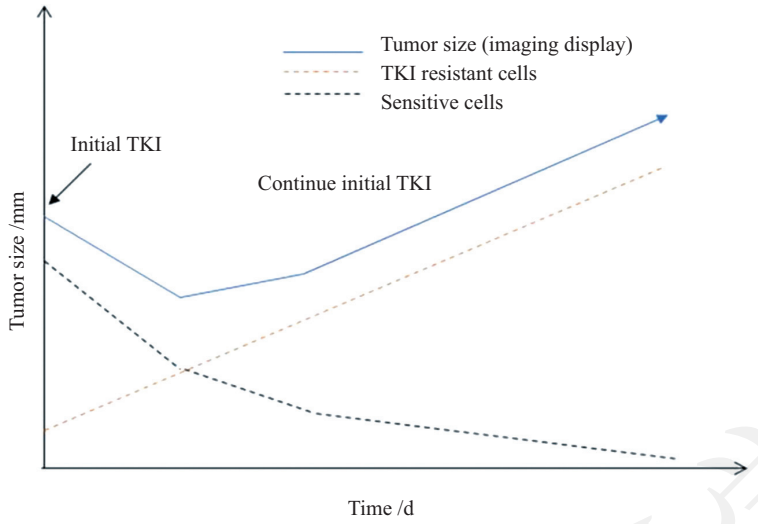
酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)是一种能抑制酪氨酸激酶活性的化合物, 它能作为三磷酸腺苷与酪氨酸激酶结合的竞争性抑制剂, 通过阻断酪氨酸激酶活性从而抑制细胞生长增殖及侵袭转移。因此TKI已被大量研发, 并作为靶向相应驱动基因所激活的癌蛋白(酪氨酸激酶蛋白), 应用于多种恶性肿瘤的临床治疗中。然而随着TKI靶向药物广泛应用, 临床实践发现, 绝大部分恶性肿瘤患者在使用TKI后迟早会出现TKI耐药。近期随着大规模平行测序如下一代基因测序(next generation sequencing, NGS)及其他分子检测技术的发展, TKI耐药机制也逐渐被揭示。目前已知的TKI耐药分子机制有致癌基因内部的二次突变如*EGFR*基因的第20号外显子*T790M*突变(*EGFR T790M*)、*KIT*基因的第13号外显子突变(*KIT E13m*)和第*17*号外显子突变(*KIT E17m*)等; 其他癌基因突变如*K-ras*、*BRAF*基因继发突变; 癌基因如肝细胞生长因子受体(cellular-mesenchymal to epithelial transition factor, *c-Met*)扩增; 旁路信号通路活化(RAS或PI3K信号通路等); 或抑癌基因如*BIM*多态性缺失, 以及病灶组织的病理类型转化等。据报道, 初始驱动基因内部的二次突变是导致TKI耐药的主要原因[18-19], 见于50%~60%的恶性肿瘤患者。近年来对于TKI耐药的处理措施包括耐药突变位点的特异性抑制剂, 或联合使用其他靶向药物如*c-Met*抑制剂, 或旁路信号通路抑制剂等, 但疗效仍不甚理想[20-21]。肿瘤演进过程中的“竞争性释放”现象存在于TKI治疗过程中, 因此本文将“竞争性释放”现象介导的TKI耐药, 以及基于此现象如何逆转TKI耐药的策略及方法作一综述。

1 “竞争性释放”现象以及恶性肿瘤内部克隆细胞亚群演变模式

1976年, Peter Nowell[22]首次提出“适者生存”的进化生物学理论适用于肿瘤演变过程, 他指出肿瘤组织是由异质性的细胞群体组成, 存在对药物不同敏感性的亚克隆细胞群, 肿瘤内部的优势细胞克隆在某种选择压力下会不断发生变化。对药物敏感的肿瘤突变亚克隆细胞在治疗下能被显著抑制, 从而对耐药亚克隆的抑制作用减弱, 耐药亚克隆在没有竞争的环境下迅速增殖, 从而导致肿瘤细胞耐药[15,20-21](图1)。这一观点的提出给肿瘤TKI的治疗策略和克服耐药提供了新的方向, 将肿瘤治疗从静态转变成动态监测肿瘤和相应的药物调整过程, 即根据肿瘤内部细胞亚群的克隆性动态变化制定新的治疗方法和策略。

近年来, 随着TKI药物的不断研制和开发, 大大提高了敏感基因突变的恶性肿瘤患者的治疗疗效, 如吉非替尼和厄洛替尼能够有效治疗*EGFR*敏感突变的肺腺癌患者, 伊马替尼治疗显著延长了*c-KIT*基因外显子9及11基因突变的胃肠间质瘤患者的生存期。但在上述靶向治疗过程中, 最终会因肿瘤细胞内部出现继发耐药突变而导致靶向治疗失败[6,7,9-11]。

研究表明, 肿瘤内部的不同细胞克隆亚群在TKI治疗过程中呈现动态变化, 导致肿瘤演化的不同模式(图2)。近期研究发现, TKI治疗可导致耐药细胞克隆的竞争性释放, 而随后一系列基础研究和临床实践也证实了通过对TKI药物的不同使用策略, 利用肿瘤内部异质性细胞群体的竞争性抑制的特点, 可延缓或逆转TKI耐药, 进而控制肿瘤生长速度,



初始使用TKI时, 敏感突变的亚克隆细胞群体数目减少, 肿块缩小; 随着TKI的持续使用, 敏感突变亚克隆受抑制; 而相应地, 耐药细胞亚克隆群体因失去“竞争压力“而释放呈进行性增加, 导致肿瘤增大, 从而产生继发TKI耐药。

When TKI is initially used, the number of sensitive cloned subcloned cells is reduced and the tumor size is reduced;Sensitive mutant subclones are inhibited with the continued use of TKI; Correspondingly, the subcloned population of drug-resistant cells showed a progressive increase in the release of “competitive stress”, resulting in an increase in tumors, resulting in secondary TKI resistance.

图1　耐药细胞克隆的“竞争性释放”示意图

Fig.1　Competitive release phenomenon of TKI resistant cells

延长患者总体生存期。

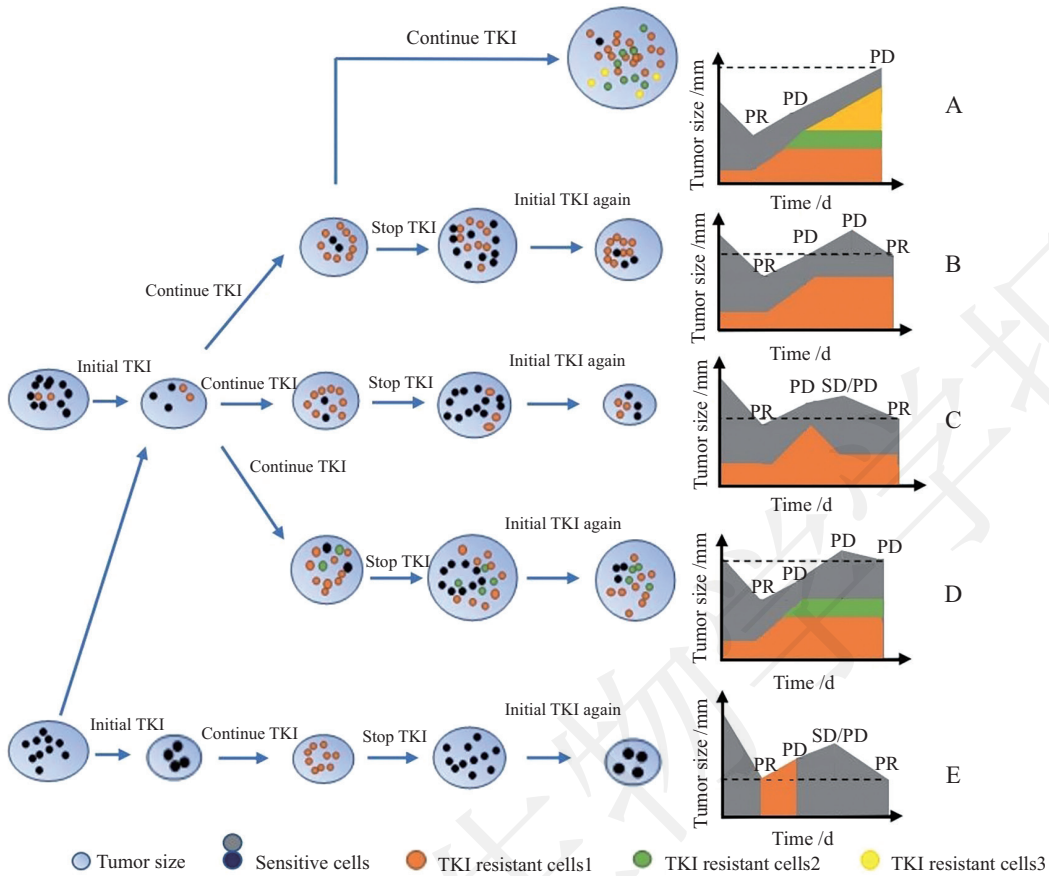
2　EGFR-TKI靶向治疗后耐药产生的“竞争性释放”现象

文献表明, 多达60%的肺腺癌患者在接受第一代EGFR-TKI治疗过程中发生20号外显子的*T790M*二次突变。然而, 在EGFR-TKI治疗前的NSCLC患者组织标本中即可检测到低丰度的T790M突变, 检测阳性率30%~80%[19]。进一步研究发现, 在第一代EGFR-TKI治疗过程中, 敏感*EGFR*突变被显著抑制, 原有低丰度的*T790M*突变被竞争性释放, 成为肿瘤内部的优势细胞克隆, 从而导致第一代TKI耐药[23]。

Hata等[24-25]研究发现, 当TKI耐药而停药后, 原有肿瘤组织*EGFR T790M*的丰度显著减少甚至消失。用NGS技术动态监测同一组织标本(包括原发的NSCLC组织、中枢神经系统和胸腔积液等)的基因变化, 结果发现, 部分患者*T790M*的丰度随着第一代TKI使用时间的延长而逐渐升高, 当停止使用第一代EGFR-TKI时, *T790M*细胞克隆显著减少甚至消失, 肿瘤细胞因此恢复对第一代EGFR-TKI的敏感性。体外实验也进一步发现[23], 将对EGFR-TKI敏感突变的*PC-9*细胞与不同比例的耐药EGFR *T790M*细胞混合之后, 在无EGFR-TKI干预下, 细胞多次传代后, *T790M*阳性细胞的比例逐渐减少, 直至消失。同时研究者还发现, 肿瘤细胞对第一代EGFR-TKI的敏感性与*T790M*阳性细胞比例呈负相关; *T790M*比例低于10%不影响细胞对一代EGFR-TKI的敏感性, 若*T790M*细胞比例大于25%, 则对一代EGFR-TKI耐药。

但是, 与上述观念不同的是, Kodama[26]报道了3例病例, 即使停止一代TKI药物, 且*T790M*丰度值下降或者消失, 但患者仍对原TKI耐药。

除T790M突变外, 另一导致一代TKI耐药的主要机制是*c-Met*基因扩增突变[27]。*c-Met*扩增使*ERBB3*受体磷酸化, 继而活化PI3K/AKT信号级联反应, 导致肿瘤细胞持续增殖。在EGFR-TKI耐药患者中, 有5%~22%的样本中检测到*c-Met*基因扩增, 其中40%患者*c-Met*扩增和*T790M*突变共存, 在约3%未经治疗的*EGFR*敏感突变患者中也检测到了*c-Met*基因扩增[27-29]。Womack[30]报道了1例*EGFR L858R*敏感突变的肺腺癌患者, 在服用厄洛替尼后, 因出现*c-Met*扩增突变导致厄洛替尼耐药, 患者因此停用厄洛替尼, 接受了化疗的临床试验; 在数周期化疗后, 患者第二次疾病进展(新出现右侧胸腔积液), 再次NGS检测活检组织, 结果显示, *c-Met*扩增倍数较前明显下降(此时已停用厄洛替尼10个月); 进一



肿瘤由敏感细胞克隆以及耐药细胞克隆群组成或者仅有敏感细胞组成; 在初始接受TKI治疗时, 肿瘤内部的敏感细胞受抑制, 肿瘤缩小(疗效评价PR)。继续TKI治疗后, 肿瘤内部将可能出现以下几种演化模式。A: 肿瘤内部出现多种耐药细胞克隆亚群, 并在持续TKI的使用下, 耐药细胞克隆数进行性增多, 肿瘤增大(疗效评价PD)。B: 肿瘤内部出现优势耐药细胞克隆亚群, 导致肿瘤增大(疗效评价PD); 停止TKI后, 敏感细胞恢复生长优势, 肿瘤进一步增大(疗效评价PD); 此时再次使用原TKI时, 肿瘤因敏感细胞再次被抑制而缩小(疗效评价PR)。C: 肿瘤内部出现优势耐药细胞克隆亚群, 导致肿瘤增大(疗效评价PD); 停止TKI后, 敏感细胞快速生长, 而耐药细胞克隆因失去“竞争性释放”的优势出现丰度下降, 肿瘤稍有增大(疗效评价SD或PD); 此时再次使用原TKI时, 肿瘤因敏感细胞再次被抑制而缩小(疗效评价PR)。D: 肿瘤内部出现多种耐药细胞克隆亚群, 导致肿瘤增大(疗效评价PD); 停止TKI后, 敏感细胞快速生长, 而原多种耐药细胞克隆亚群仍存在, 肿瘤进行性增大(疗效评价PD); 此时再次使用原TKI时, 尽管敏感细胞被抑制, 但因存在的耐药细胞亚群, 肿瘤呈现异质性反应, 总体疗效评价为SD。E: 肿瘤内部原有的敏感细胞全部被抑制, 而耐药细胞克隆亚群因“竞争性释放”快速增殖, 导致肿瘤增大(疗效评价PD); 停止TKI后, 敏感细胞急速生长, 耐药细胞克隆因失去“竞争性释放”的优势而消退, 肿瘤基本稳定或稍增大(疗效评价SD或PD); 此时再次使用原TKI时, 敏感细胞再次被显著抑制, 肿瘤明显缩小(疗效评价PR)。

Tumors consist of sensitive subclones and resistant subclones or only sensitive subclones; at the initial TKI treatment, sensitive cells inside the tumor are inhibited and the tumor shrinks(the efficacy is evaluated as PR). Continuing TKI treatment, the following evolution patterns may occur within the tumor. A: multiple drug-resistant cell clonal subpopulations appear within the tumor, and the number of drug-resistant cell clones increases progressively with the use of TKI, and tumor enlargement (the efficacy is evaluated as PD). B: a subpopulation of dominant drug-resistant cells appears inside the tumor, leading to tumor enlargement (the efficacy is evaluated as PD). Stopping the TKI, the sensitive cells recovered their growth advantage and the tumor further increased (the efficacy evaluation PD); at this time, when the original TKI is used again, the tumor shrinks due to the suppression of the sensitive cells again (the therapeutic effect was evaluated by PR). C: a subpopulation of dominant drug-resistant cells appears inside the tumor, leading to tumor enlargement (effectiveness evaluation PD); stopping TKI, sensitive cells grow rapidly, while drug-resistant cell clones show a decrease in abundance due to the loss of “competitive release”, and tumors increase slightly (the efficacy is evaluated as SD or PD); at this time, when the original TKI is used again, the tumor shrinks due to the suppression of the sensitive cells again (the therapeutic effect was evaluated by PR). D: multiple drug-resistant cell clonal subpopulations appear inside the tumor, leading to tumor enlargement (effectiveness evaluation PD); after stopping TKI, sensitive cells grow rapidly, while the original multi-drug resistant cell clone sub-population still exists, and the tumor progresses progressively (Efficacy evaluation PD); at this time, when the original TKI is used again, although the sensitive cells are inhibited, the tumor shows a heterogeneous reaction due to the presence of the drug-resistant subpopulation(the overall therapeutic effect is evaluated as SD). E: the original sensitive cells in the tumor are all inhibited, and the drug-resistant cell clonal subpopulation rapidly proliferates due to “competitive release”, resulting in tumor enlargement (effectiveness evaluation PD); stopping TKI, sensitive cells rapidly grow, resistant cell clones Due to the loss of the advantage of “competitive release”, the tumor is basically stable or slightly increased (the efficacy evaluation SD or PD); at this time, when the original TKI is used again, the sensitive cells are again significantly inhibited, and the tumor is significantly reduced (the therapeutic evaluation PR).

图2 肿瘤缓慢进展后TKI持续使用或间歇使用肿瘤演化模式简图

Fig.2 Schematic representation of tumor evolution after tumor slow progression and receiving TKI treatment

步研究发现, 含*c-Met*扩增的肿瘤细胞数目显著减少; 因此重新给予厄洛替尼治疗, 厄洛替尼再次治疗2个月后, PET-CT显示肿块缩小, 疗效评估部分缓解(partial response, PR)。4个月后, 患者病情广泛进展, 此时再次检测发现*c-Met*基因拷贝数较前升高。上述病例结果表示, *c-Met*基因扩增丰度值在EGFR-TKI抑制其敏感突变的情况下呈现“竞争性释放”现象。

3 基于“竞争性释放”现象逆转TKI靶向治疗耐药的方法和策略

TKI治疗敏感基因突变型的恶性肿瘤取得了可喜的临床疗效, 探讨如何延缓或逆转TKI耐药, 尽可能最大限度地发挥TKI治疗作用, 并改善用药经济学已成为当前研究的重点和热点。基于上述”竞争性释放”现象进行克服或逆转TKI靶向治疗耐药的方法或措施主要体现在以下几个方面:

3.1 不同的给药方式延缓耐药的产生

Jakob等[31]发现, 相对于普通的治疗剂量, 间断高剂量TKI给药会更好抑制肿瘤细胞生长。动物实验发现, 当给予敏感突变细胞间断的高剂量时(TKI 200 mg/kg每隔一天给药), 肿瘤缩小的速度要明显快于常规给药剂量(30 mg/kg/天), 且药物相关不良反应并未增加。Juliann等[23]根据肿瘤细胞的进化模型进一步研究了不同的给药方式对细胞耐药的影响; 他们通过计算细胞增长速率和死亡率来表示不同剂量的给药模式下肿瘤发生耐药的情况; 研究发现, 敏感型NSCLC细胞在持续TKI低剂量联合高剂量冲击治疗可延缓获得性*T790M*突变的发生。高峰等[32]发现, 当TKI联合化疗时, 先给予化疗, 再续以TKI治疗可延缓TKI耐药发生。

3.2 进展后第一代TKI的再次使用

传统意义上, 一旦肿瘤复发或进展, 就意味着对目前治疗耐药, 因此常常需要更改新的治疗方案。但基于“竞争性释放”的肿瘤细胞演化现象, 敏感突变的细胞克隆在持续的TKI压力下被显著抑制, 耐药细胞株被“竞争性释放”而成为优势克隆, 快速增殖; 而后者在TKI被撤离后因失去“竞争性释放”优势而被“复燃”的敏感细胞所替代, 此时肿瘤即恢复对原TKI的抑制作用。

近期文献表明, 一些*c-KIT*基因敏感突变的GIST患者在对一线伊马替尼耐药后, 通过停用伊马替尼或改用其他药物, 肿瘤重新获得了对伊马替尼敏感性[33]。最近Bruno等[34]报道, 将伊马替尼重新用于59例曾先后接受过伊马替尼、舒尼替尼以及瑞格菲尼等TKI的GIST患者中; 结果发现, 5例达到了PR, 32例病情稳定(stable disease, SD), 疾病控制率达52%; 中位疾病进展时间(time to progression, TTP)为5个月, OS约11个月。同样地, BFR14试验[35]也证实了伊马替尼重新使用的有效性和安全性, 对术后辅助服用了伊马替尼的患者, 当患者出现疾病进展(progression disease, PD)时都重新再次接受伊马替尼治疗, 疾病控制率大于92%。Kang等[36]也进行了一项伊马替尼重新使用的临床观察, 其PFS(较对照组)延长了2倍, 并提高了26.7%患者的12周疾病控制率, 且患者的耐受性良好。Satoh等[37]报道了1例晚期NSCLC患者成功的接受TKI的初始治疗以及再次治疗。同样地, 其他研究也陆续报道了成功将原TKI再次使用于初始TKI耐药的恶性肿瘤患者中; 为此, 我们将临床上TKI耐药后再次使用的相关文献及患者信息进行了简要总结(表1)。

3.3 第一代TKI再次使用的策略和方法

3.3.1 继续原第一代TKI治疗(常规剂量或冲击治疗) Otsuka等[38]研究发现, 24名接受第一代TKI治疗失败后的患者再次接受原TKI治疗, 单用或联合使用贝伐珠单抗, 其中有效缓解率为13%, 疾病控制率达到88%。同样地, Hata等[39]报道59名*EGFR*突变的肺腺癌患者第一代TKI治疗耐药后间隔一段时间再次第一代TKI药物, 其中12位获得部分缓解(partial response, PR), 23例患者SD, 疾病控制率为(disease control rate, DCR) 59.3%。Cappuzzo等[40]评估吉非替尼再使用的疗效, 他们发现, 患者在接受吉非替尼再次治疗时, 能够给患者带来生存益处的同时, 并没有带来新的毒副反应。同样, Zhao[41]及Nishino等[42]各自的研究中也分别证实了, 再次使用原TKI治疗可使患者获得生存获益。Oh等[43]入组了20名吉非替尼治疗失败的晚期NSCLC患者再次予以吉非替尼治疗, TTP为3.3个月, DCR达到75%。宋勇[44]等选取了46名接受过吉非替尼治疗失败的晚期NSCLC患者, 出现耐药后停药并接受4周期的二线化疗, 然后再次予以原剂量的吉非替尼再次治疗, 其中DCR达到69.8%, mPFS为4.4月。Wang等[45]报道了1例NSCLC患者在接受埃克替尼治疗后疾病出现进展, 重新活检后开始使用AZD9291, 后来病情再次进展

表1 一线TKI耐药后再次使用原TKI的患者简要信息表

Table 1 Brief information of patients accepted initial TKI rechallenge

疾病 Disease	突变基因 Mutant gene	初始TKI Initial TKI	耐药机制 Resistance mechanism	停TKI后治疗方法及维持时间 Treatments and time after TKI discontinuation	再次使用的TKI TKI rechallenge	治疗评估 Therapeutic evaluation		3/4级副反应 3/4 Degree adverse effects	试验时间 Experiments duration	试验类型 Experiments type	作者 Authors	试验人数 Patients number	试验来源 Trail source
						中位无进展生存时间 PFS /m	疾病控制率 DC /%						
NSCLC	*EGFR*	Gefitinib	S	W+C(2.8 m)	Gefitinib	4.4	69.8	No	2014—2016	Clinical trial II	Song[44]	46	CHN
NSCLC	*EGFR*	Erlotinib/Gefitinib	S	W(N)	Erlotinib+VEGF/VEGFR	4.1	88	No	2010—2014	Clinical trial II	Otsuka[38]	24	JP
NSCLC	*EGFR*	Erlotinib	S	W+C(2 m)	Erlotinib	11	N	No	2007—2010	Clinical trial II	Guo[64]	1	CHN
NSCLC	*EGFR*	Gefitinib	S	W+C(2 m)	Gefitinib	8	N	No	2006—2009	Case report	Guo[64]	1	CHN
NSCLC	*EGFR*	Icotinib	S	W+ Osimertinib (15m)	Icotinib	8	N	No	2015—2018	Case report	Wang[45]	1	CHN
NSCLC	*EGFR*	Icotinib	S	W(7.75 m)	Icotinib+VEGF/VEGFR	4.6	100	No	2015—2016	Clinical trial II	Li[59]	14	CHN
NSCLC	*EGFR*	Erlotinib	S	W(N)	Erlotinib+VEGF/VEGFR	4.6	65	No	2010—2017	Clinical trial II	Qu[58]	40	CHN
NSCLC	*EGFR*	Gefitinib	S	W (N)	Erlotinib	6	29.2	No	2007—2012	Clinical trial II	Kaira[50]	106	JP
NSCLC	*EGFR*	Gefitinib	S	W(N)	Erlotinib	3.3	44	No	2009—2012	Clinical trial II	Ying[51]	96	CHN
NSCLC	*EGFR*	Erlotinib	B	W+C(14 m)	Erlotinib	2	N	No	2006—2011	Case report	Womack[30]	1	US
NSCLC	*EGFR*	Gefitinib	S	W+C(N)	Erlotinib	2	44	No	2008—2009	Clinical trial II	Hata[39]	125	JP
GIST	*KIT*	Imatinib+ Sunitinib+Regorafenib	S	WN)	Imatinib	5	52	No	2015—2017	Clinical trial II	Vincenzi[34]	59	IT
GIST	*KIT*	Imatinib	S	W(N)	Imatinib	1.8	26.7	No	2010—2013	Clinical trial III	Kang[36]	40	KP
NSCLC	*EGFR*	Gefitinib/Erlotinib	S	A(N)	Gefitinib/Erlotinib	6	45.2	No	2013—2014	Clinical trial II	Zhu[46]	42	CHN
NSCLC	*EGFR(L858R)*	Erlotinib	S	A(0)	Erlotinib	Months	N	No	2009—2011	Case report	Kuiper[47]	1	NL
NSCLC	*EGFR(Del-19)*	Erlotinib	S	A(0)	Erlotinib	Months	N	No	2008	Case report	Kuiper[47]	1	NL
NSCLC	*EGFR*	Erlotinib	S	A(N)	Erlotinib	2.7	77	No	-	Retrospective analyze	Grommes[48]	9	US
NSCLC	*EGFR*	Gefitinib	S	W(N)	Erlotinib/Gefitinib	3.4	73	No	2005—2009	Clinical trial II	Watanabe[52]	11	JP
NSCLC	*EGFR*	Gefitinib/Erlotinib	S	W+C(N)	Erlotinib/Gefitinib	6	85.2	No	2010—2014	Retrospective analyze	Xia[53]	27	CHN
NSCLC	*EGFR(L858R)*	Osimertinib	N	W+C(N)	Osimertinib	1	N	No	N	Case report	Satoh[37]	1	JP
Melanoma	*BRAF*	Dabrafenib	S	W+I(7m)	Vemurafenib	4	N	No	2009—2012	Case report	Ame´lie[65]	1	BE
Melanoma	*BRAF*	Dabrafenib	S	W(8 m)	Dabrafenib	5	N	No	2000—2011	Case report	Ame´lie[65]	1	BE
Melanoma	*BRAF*	Dabrafenib +Trametinib	S	W (5 d)	Dabrafenib+Trametinib	5	N	No	2011—2016	Case report	Ibrahim[66]	1	FR
Melanoma	*BRAF*	Dabrafenib+ Trametinib	S	W (N)	Dabrafenib+Trametinib	5.2	100	No	2013—2016	Clinical trial II	Rogiersa[67]	4	BE
Melanoma	*BRAF*	Dabrafenib	S	W+I(N)	Dabrafenib	6	80	No	2010—2014	Clinical trial II	Roux[68]	10	FR
Melanoma	*BRAF*	Dabrafenib	S	W(N)	Dabrafenib	4.9	72	No	2014—2016	Clinical trial II	Schreuer[69]	25	BE

S: 原突变基因内二次突变; P: 旁路信号通路活化; W: 停药; C: 化疗 I: 免疫治疗; A: 调整剂量 m: 月; d: 天; N: 不确定。

S: secondary mutation ; B: bypass signaling pathway activation; W: withdraw drug; C: chemotherapy; I: immunotherapy; A: adjustment; M: month; D: day; N: not sure.

后停止AZD9291并重新使用埃克替尼治疗获得显著疗效(PFS长达8个月)。

为明确再次使用TKI时的剂量, 朱艳哲等[46]给予患者原TKI药物的高剂量脉冲治疗, 结果显示, PR为19.0% , DCR为45.2%, 中位PFS为6个月, 且治疗过程中患者并未出现严重不良反应。Kuiper[47]也发现高剂量脉冲的厄洛替尼再次治疗有效。Grommes[48]对9位TKI治疗失败的晚期NSCLC患者, 再次给予厄洛替尼治疗(1 500 mg/周脉冲式给药), 结果显示, 6例患者获 PR, 1例获SD, 另有2例PD。同时研究发现, 厄洛替尼剂量达到每周2 000 mg时, 患者仍可耐受或毒副作用在可控范围之内[49]。

3.3.2 *第一代TKI家族中的不同药物继续治疗* Kira[50]研究发现, 106例吉非替尼治疗失败后口服厄洛替尼的晚期NSCLC患者, 其ORR为9.9%, DCR为29.2%。进一步分析发现, 初始吉非替尼获益的患者耐药后可从厄洛替尼中获得更好疗效。应晓珍等[51]回顾分析96例一线使用吉非替尼进展后换用厄洛替尼的晚期NSCLC患者, 结果显示, PR为10.42%, DCR为62.50%, PFS为3.3个月。Hata等[39]对125例吉非替尼治疗失败的患者予以厄洛替尼继续治疗, ORR为9%、DCR为44%, 平均PFS为2.0个月; 其中32例在吉非替尼治疗失败后改用细胞毒药物治疗, 进展后再口服厄洛替尼的患者疗效更好(ORR 25%, DCR 72%, PFS 3.4个月)。Watanabe等[52]对11名吉非替尼耐药患者中再次TKI(3名患者接受原吉非替尼治疗, 8名患者改用厄洛替尼治疗), 结果显示, 1例PR, 7例SD, DCR为73%, 中位PFS约为3.4个月。

Xia等[53]纳入了27名接受过第一代TKI治疗失败的晚期NSCLC患者, 出现耐药后接受二线化疗后病情继续进展, 13名患者再次接受原TKI的同种药物治疗, 14名患者接受原TKI家族的不同药物治疗, 两组PFS差别显著, 分别为5个月、9.5个月(P<0.05), DCR分别为: 84.6%、85.7%, 两者无差别。这提示, 同一代TKI的不同种药物在再次使用时可能获得较好的PFS。

3.3.3 *原第一代TKI联合化疗* 近期, Johnson等[54]筛选了120例符合标准的第一代TKI治疗失败的NSCLC患者, 随机分成3组, 即贝伐珠单抗联合化疗、厄洛替尼联合贝伐珠单抗和单用化疗组。结果显示, 3组的中位OS分别为12.6个月、13.7个月、8.6个月, 中位PFS分别为4.8个月、4.4个月、3.0个月。研究认为, 重新使用厄洛替尼, 或联合贝伐单抗, 较单用化疗组提高患者生存期。

然而与上述结论不同的是, 潘仁凤等[55]研究发现, TKI耐药后再次使用原TKI同时联合化疗, 与单独化疗相比, 两者的PFS及OS并无差异, 而毒性反而增加。Soria等[56]将256名接受过第一代TKI失败后的NSCLC随机分为2组, 分别使用吉非替尼联合顺铂及培美曲塞, 或顺铂联合培美曲塞治疗, 结果显示, 两组的中位OS分别是17.2个月和14.8个月, 吉非替尼联合化疗组较单用化疗组具有更长OS。但吉非替尼联合化疗组更多患者出现严重不良反应。最近的一项I/II期临床试验也评估了阿霉素联合伊马替尼治疗原伊马替尼耐药的GIST患者, 其中36%的患者疾病得到控制, 提示再次使用原TKI联合化疗的应用前景[57]。

3.3.4 *原第一代TKI联合抗血管生成药物* 肿瘤血管生成是肿瘤发生侵袭及转移的必要前提, 针对抗血管内皮生长因子/抗血管内皮生长因子受体(vascular endothelial growth factor/vascular endothelial growth factor receptor, VEGF/VEGFR)的药物已经得到广泛应用。为研究TKI二次用药同时联合抗血管生成药物(重组人血管内皮抑素或贝伐珠单抗)的疗效, 屈丽岩等[58]研究40例一代TKI耐药的NSCLC患者, 再次给予原一代TKI并联合抗血管生成药物, 患者客观缓解率为22.5%, 疾病控制率为65%。患者耐受性良好, 未出现严重不良反应。Li等[59]发现, EGFR-TKI联合VEGFR抑制剂对已经产生第一代TKI耐药的NSCLC患者有效, 阿帕替尼联合原一代TKI治疗一线TKI失败的NSCLC患者可达到4.6个月的中位无进展生存期。Otsuka等[38]回顾性分析了24名一代TKI治疗失败的晚期NSCLC患者, 再次予以一代TKI同时联合贝伐珠单抗, 结果显示, 客观缓解率13%, 疾病控制率88%, 中位PFS达到4.1个月, 中位OS达到13.5个月。进一步结果发现, T790M阴性患者较阳性患者更能在该治疗方案中获益。

一项III期临床试验, 共480名一线TKI治疗失败的晚期NSCLC患者, 分为舒尼替尼联合厄洛替尼组和安慰剂+厄洛替尼组, 结果显示, 两者的中位PFS分别为3.6个月和2.0个月; ORR为10.6%和6.9%, 差异具有统计学意义, 提示舒尼替尼联合厄洛替尼组可使患者获益[60]。

4 结语

目前, 靶向药物TKI已成为敏感基因突变阳性恶性肿瘤中的一线选择方案, 但是耐药不可避免会发生。基于”竞争性释放”现象, 肿瘤内部的耐药细胞亚克隆随着第一代TKI药物的减量或撤药而显著减少甚至消失, 从而使肿瘤恢复对第一代TKI的敏感性。因此, 通过TKI使用的不同策略, 从而提高患者的DCR, 改善患者的生活剂量, 延长患者的PFS, 甚至OS, 同时改善药物经济学已成为当今研究的热点。最近文献也表明, 伊马替尼治疗失败的GIST患者中, 与瑞戈非尼相比, 伊马替尼再次使用似乎在PFS延长, 特别是低的不良反应率中占优势[61]。另外, 靶向*EGFR T790M*突变的第三代TKI治疗进展后, 停药一段时间后再次使用也能让患者获益[37]。但是, 如何全面并动态监测肿瘤内部细胞克隆的变化, 基于不同肿瘤的分子特点筛选TKI再次使用的受益人群, 以及TKI再次给药的时机及剂量等个体化策略的选择, 均尚待进一步研究。另外需要警惕的是TKI停药后的肿瘤快速进展(即疾病复燃或爆发)[62], 指的是在停止使用TKI后, 后续治疗开始之前, 肿瘤突然进展至需要住院治疗或者是导致患者死亡的情况, 其发生率为4%~23%, 发生时间约在停止使用TKI后8天左右; 但其发生机制目前尚不清楚。上述情况更多见于初次使用TKI治疗显效时间短, 或者治疗前有脑转移或者胸膜转移的患者。因此, 我们应该在患者停止TKI治疗时进行密切观察和随访, 及时处理因停用TKI而导致的疾病复燃或爆发, 此时需要尽快再次给予患者原TKI药物, 大部分患者病情会得到控制[63]。

参考文献 (References)

1 Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, *et al*. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016; 66(4): 271-89.

2 Mitsudomi T, Yatabe Y. Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. Cancer Sci 2007; 98(12): 1817-24.

3 Douillard JY, Ostoros G, Cobo M, Ciuleanu T, McCormack R, Webster A, *et al*. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. Br J Cancer 2014; 110(1): 55-62.

4 Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, *et al*. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010; 11(2): 121-8.

5 Tatematsu A, Shimizu J, Murakami Y, Horio Y, Nakamura S, Hida T, *et al*. Epidermal growth factor receptor mutations in small cell lung cancer. Clin Cancer Res 2008; 14(19): 6092-6.

6 Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, *et al*. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003; 299(5607): 708-10.

7 Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, *et al*. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and *in vitro* sensitivity to imatinib. J Clin Oncol 2005; 23(23): 5357-64.

8 Heinrich MC, Rubin BP, Longley BJ, Fletcher JA. Biology and genetic aspects of gastrointestinal stromal tumors: KIT activation and cytogenetic alterations. Hum Pathol 2002; 33(5): 484-95.

9 Hodis E, Watson IR, Kryukov GV, Arold ST, Imielinski M, Theurillat JP, *et al*. A landscape of driver mutations in melanoma. Cell 2012; 150(2): 251-63.

10 Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, *et al*. Mutations of the BRAF gene in human cancer. Nature 2002; 417(6892): 949-54.

11 Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, *et al*. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009; 361(10): 958-67.

12 Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczã©Sna A, Juhã sE, *et al*. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncology 2010; 11(6): 500-1.

13 Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362(25): 2380-8.

14 Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13(3): 239-46.

15 Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, *et al*. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 2005; 352(8): 786-92.

16 Kwak EL, Raffaella S, Bell DW, Nadia GH, Okimoto RA, Brannigan BW, *et al*. Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. PNAS 2005; 102(21): 7665-70.

17 Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, *et al*. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2005; 2(3): e73.

18 Inukai M, Toyooka S, Ito S, Asano H, Ichihara S, Soh J, *et al*. Presence of epidermal growth factor receptor gene T790M mutation as a minor clone in non-small cell lung cancer. Cancer Res 2006; 66(16): 7854-8.

19 Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, *et al*. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci USA 2008; 105(6): 2070-5.

20 Takeda M, Okamoto I, Tsurutani J, Oiso N, Kawada A, Nak-

agawa K. Clinical impact of switching to a second EGFR-TKI after a severe AE related to a first EGFR-TKI in EGFR-mutated NSCLC. Jpn J Clin Oncol 2012; 42(6): 528-33.

21 Enriquez-Navas PM, Wojtkowiak JW, Gatenby RA. Application of evolutionary principles to cancer therapy. Cancer Res 2015; 75(22): 4675-80.

22 Nowell PC. The clonal evolution of tumor cell populations. Science 1976; 194: 23-8.

23 Chmielecki J, Foo J, Oxnard GR, Hutchinson K, Ohashi K, Somwar R, *et al*. Optimization of dosing for EGFR-mutant non-small cell lung cancer with evolutionary cancer modeling. Sci Transl Med 2011; 3(90): 90ra59.

24 Hata A, Katakami N, Yoshioka H, Takeshita J, Tanaka K, Nanjo S, *et al*. Rebiopsy of non-small cell lung cancer patients with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor: comparison between T790M mutation-positive and mutation-negative populations. Cancer 2013; 119(24): 4325-32.

25 Hata A, Katakami N, Yoshioka H, Kaji R, Masago K, Fujita S, *et al*. Spatiotemporal T790M heterogeneity in individual patients with EGFR-mutant non-small-cell lung cancer after acquired resistance to EGFR-TKI. J Thorac Oncol 2015; 10(11): 1553-9.

26 Tatsuya K, Keisuke W, Masaharu S, Takeshi K. No therapeutic effect of epidermal growth factor receptor tyrosine kinase inhibitor retreatment despite T790M disappearance: case report of 3 cases. Chemotherapy 2018; 63(4): 198-202.

27 Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, *et al*. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007; 316(5827): 1039-43.

28 Bean J, Brennan C, Shih JY, Riely G, Viale A, Wang L, *et al*. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci USA 2007; 104(52): 20932-7.

29 Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, *et al*. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011; 3(75): 75ra26.

30 Womack JP, Varella-Garcia M, Camidge DR. Waxing and waning of MET amplification in EGFR-Mutated NSCLC in response to the presence and absence of erlotinib selection pressure. J Thorac Oncol 2015; 10(12): e115-8.

31 Schottle J, Chatterjee S, Volz C, Siobal M, Florin A, Rokitta D, *et al*. Intermittent high-dose treatment with erlotinib enhances therapeutic efficacy in EGFR-mutant lung cancer. Oncotarget 2015; 6(36): 38458-68.

32 高峰, 张泽峰, 王涛, 王瑞. EGFRTKIs联合化疗的给药顺序对NSCLC细胞促凋亡的影响. 中国现代医学杂志(Gao Feng, Zhang Zefeng, Wang Tao, Wang Rui. Effect of EGFR-TKIs and chemotherapy combinations and administration sequence on apoptosis of NSCLC cells. China Journal of Modern Medicine) 2018; 28(14): 30-6.

33 Heinrich MC, Corless CL, Blanke CD, Demetri GD, Joensuu H, Roberts PJ, *et al*. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006; 24(29): 4764-74.

34 Vincenzi B, Nannini M, Badalamenti G, Grignani G, Fumagalli E, Gasperoni S, *et al*. Imatinib rechallenge in patients with advanced gastrointestinal stromal tumors following progression with imatinib, sunitinib and regorafenib. Ther Adv Med Oncol 2018; 10: 1-8.

35 Blay JY, Perol D, Le Cesne A. Imatinib rechallenge in patients with advanced gastrointestinal stromal tumors. Ann Oncol 2012; 23(7): 1659-65.

36 Kang YK, Ryu MH, Yoo C, Ryoo BY, Kim HJ, Lee JJ, *et al*. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncology 2013; 14(12): 1175-82.

37 Satoh S, Shiroyama T, Tamiya M, Nasu S, Tanaka A, Morita S, *et al*. Successful osimertinib rechallenge after osimertinib-induced pneumonitis in a patient with lung adenocarcinoma. Respir Med Case Rep 2018; 23: 68-70.

38 Otsuka K, Hata A, Takeshita J, Okuda C, Kaji R, Masago K, *et al*. EGFR-TKI rechallenge with bevacizumab in EGFR-mutant non-small cell lung cancer. Cancer Chemother Pharmacol 2015; 76(4): 835-41.

39 Hata A, Katakami N, Yoshioka H, Fujita S, Kunimasa K, Nanjo S, *et al*. Erlotinib after gefitinib failure in relapsed non-small cell lung cancer: clinical benefit with optimal patient selection. Lung Cancer 2011; 74(2): 268-73.

40 Cappuzzo F, Morabito A, Normanno N, Bidoli P, Del Conte A, Giannetta L, *et al*. Efficacy and safety of rechallenge treatment with gefitinib in patients with advanced non-small cell lung cancer. Lung Cancer 2016; 99: 31-7.

41 Zhao ZR, Li W, Long H. Readministration of EGFR tyrosine kinase inhibitor in non-small cell lung cancer patients after initial failure, what affects its efficacy? Sci Rep 2014; 4: 5996.

42 Nishino K, Imamura F, Morita S, Mori M, Komuta K, Kijima T, *et al*. A retrospective analysis of 335 Japanese lung cancer patients who responded to initial gefitinib treatment. Lung Cancer 2013; 82(2): 299-304.

43 Oh IJ, Ban HJ, Kim KS, Kim YC. Retreatment of gefitinib in patients with non-small-cell lung cancer who previously controlled to gefitinib: a single-arm, open-label, phase II study. Lung Cancer 2012; 77(1): 121-7.

44 Song Y, Wu YL, Cao LJ, Chen JH, Ma ZY, Cui JW, *et al*. Efficacy and safety of gefitinib as third-line treatment in NSCLC patients with activating EGFR mutations treated with first-line gefitinib followed by second-line chemotherapy: a single-arm, prospective, multicenter phase II study (RE-CHALLENGE, CTONG1304). Am J Clin Oncol 2019; 19(1): 131

45 Wang J, Chen J. Positive response to Icotinib in metastatic lung adenocarcinoma with acquiring EGFR Leu792H mutation after AZD9291 treatment: a case report. BMC Cancer 2019; 19: 131.

46 朱艳哲, 潘跃银, 杜瀛瀛. 高剂量吉非替尼或厄洛替尼脉冲治疗继发性耐药晚期非小细胞肺癌疗效及安全性的单中心、单臂、II期临床研究? 临床肿瘤学杂志(Zhu Yanzhe, Pan Yueyin, Du Yingying, Liu Hu, Ma Tai, Shen Yuanyuan. A single center, single arm and phase II clinical trail: efficacy and safety of pulsatile administration of high-dose gefitinib or erlotinib for advanced NSCLC patients with secondary drug resistance. Chinese Clinical Oncology) 2015: 20(12): 1103-9.

47 Kuiper JL, Smit EF. High-dose, pulsatile erlotinib in two NSCLC

patients with leptomeningeal metastases--one with a remarkable thoracic response as well. Lung Cancer 2013; 80(1): 102-5.

48 Grommes C, Oxnard GR, Kris MG, Miller VA, Pao W, Holodny AI, *et al*. “Pulsatile” high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. Neuro Oncol 2011; 13(12): 1364-9.

49 Milton DT, Azzoli CG, Heelan RT, Venkatraman E, Gomez JE, Kris MG, *et al*. A phase I/II study of weekly high-dose erlotinib in previously treated patients with nonsmall cell lung cancer. Cancer 2006; 107(5): 1034-41.

50 Kaira K, Yamamoto N. Erlotinib after failure of gefitinib treatment of more than 6 months in advanced non-small cell lung cancer. Onkologie 2012; 35(1/2): 8-9.

51 应晓珍. 厄洛替尼挽救治疗吉非替尼治疗失败的晚期非小细胞肺癌的疗效. 实用药物与临床(Ying Xiaozhen. Efficacy of erlotinib salvage treatment for gefitinib treatment failure on advanced non-small cell lung cancer. Practical Pharmacy And Clinical Remedies) 2013; 16(9): 859-61.

52 Watanabe S, Tanaka J, Ota T, Kondo R, Tanaka H, Kagamu H, *et al*. Clinical responses to EGFR-tyrosine kinase inhibitor retreatment in non-small cell lung cancer patients who benefited from prior effective gefitinib therapy: a retrospective analysis. BMC Cancer 2011; 11: 1.

53 Xia GH, Zeng Y, Fang Y, Yu SR, Wang L, Shi MQ, *et al*. Effect of EGFR-TKI retreatment following chemotherapy for advanced non-small cell lung cancer patients who underwent EGFR-TKI. Cancer Biol Med 2014; 11(4): 270-6.

54 Johnson BE, Kabbinavar F, Fehrenbacher L, Hainsworth J, Kasubhai S, Kressel B, *et al*. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2013; 31(31): 3926-34.

55 潘仁凤, 边吉来, 王玫玫, 金春梅. 肺癌EGFR-TKI治疗失败后化疗与化疗联合EGFR-TKI疗效分析. 医学与哲学(Pan Renfeng, Bian Jilai,Wang Meimei, Jin Chunmei. Efficacy analysis of chemotherapy combined EGFR-TKI in lung cancer after EGFR-TKI treatment failure. Medicine & Philosophy) 2016; 37(8B): 22-3.

56 Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, *et al*. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol 2015; 16(8): 990-8.

57 Agulnik M, Giel JL. Understanding rechallenge and resistance in the tyrosine kinase inhibitor era: imatinib in gastrointestinal stromal tumor. Am J Clin Oncol 2014; 37(4): 417-22.

58 屈丽岩, 康晓艳, 宋霞. 抗血管生成药物联合EGFR-TKI在晚期NSCLC治疗中的应用. 国际肿瘤学杂志(Qu Liyan, Kang Xiaoyan, Song Xia. Appliation of the combination of antiangiogenic agents and EGFR-TKIs in advanced NSCLC treatment, Journal of International Oncology) 2017; 4(1): 57-9.

59 Li F, Zhu T, Cao B, Wang J, Liang L. Apatinib enhances antitumour activity of EGFR-TKIs in non-small cell lung cancer with EGFR-TKI resistance. Eur J Cancer 2017; 84: 184-92.

60 Scagliotti GV, Krzakowski M, Szczesna A, Strausz J, Makhson A, Reck M, *et al*. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial. J Clin Oncol 2012; 30(17): 2070-8.

61 Shah K, Chan KKW, Ko YJ. A systematic review and network meta-analysis of post-imatinib therapy in advanced gastrointestinal stromal tumour. Curr Oncol 2017; 24(6): e531-9.

62 Park EH, Lee HY, Kim JW, Yeo CD. Disease flare after discontinuing gefitinib in a patient with lung adenocarcinoma and concomitant epithelial growth factor receptor mutation and anaplastic lymphoma kinase translocation. J Thorac Dis 2017; 9(6): E543-6.

63 Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res 2011; 17(19): 6298-303.