

表皮生长因子受体酪氨酸激酶抑制剂在治疗非小细胞肺癌中的研究进展

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摘要:表皮生长因子受体酪氨酸激酶抑制剂(EGFR-TKI)至今已上市近二十年。第一代 EGFR-TKI 在提高 EGFR 突变晚期非小细胞肺癌(NSCLC)的客观缓解率(ORR)、延长无进展生存期(PFS)方面起了重大的贡献。第二代 EGFR-TKI 在延长总生存期(OS)方面带来了惊喜。第三代 EGFR-TKI 克服了第一二代药物的耐药,其一线 PFS 可能打破现有治疗的格局。第四代 EGFR-TKI 已在研发中且 EGFR-TKI 研究已扩展到术后辅助治疗领域,期待其进一步的发展。

关键词:表皮生长因子受体酪氨酸激酶抑制剂;非小细胞肺癌;治疗

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Research Progress of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor in Non-small Cell Lung Cancer

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Abstract: The epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) have been available on the market for nearly twenty years. The first generation EGFR-TKI made a significant contribution by increasing objective response rate (ORR) and prolonging progression free survival (PFS) in patients with EGFR mutation-positive non-small cell lung cancer. The second generation EGFR-TKI surprisingly extended the overall survival (OS). The third generation EGFR-TKI overcame the resistance to the first and the second generation EGFR-TKI. And its first-line PFS will be likely to break the existing treatment patterns. The fourth generation EGFR-TKI is being developed to overcome the resistant to third generation and the clinical trails will be extended to postoperative adjuvant therapy. The further development of EGFR-TKIs is expected.

Key words: epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI); non-small cell lung cancer (NSCLC); therapy

表皮生长因子受体(epidermal growth factor receptor, EGFR)由胞外区、跨膜结构区及含有酪氨酸激酶及磷酸化位点的胞内区三个部分组成。配体与胞外区结合后,胞内区酪氨酸激酶激活,残基磷酸化,信号传导通路(主要是PI3K/AKT/mTOR通路、RAS/RAF/MAPK通路、JAK通路及STAT通路^[1])级联放大,在各类细胞特别是在上皮细胞的增殖、分化和迁移中起了重要作用^[2]。

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编码 EGFR 的基因位于 7 号染色体的短臂 12-14 区,由 28 个外显子组成。肺癌患者外显子 18-21 区常发生突变,主要包括:18、20 及 21 区的点突变(G719X,占 3%;T790M,占 1%;L858R,占 35%)和 19 区的缺失突变(占 45%)^[3]等。突变使 EGFR 在没有配体激活的情况下,酪氨酸激酶活性增加 50 倍,残基磷酸化增加,下游信号传导增强,促进肿瘤的发展^[4]。大约 15%的高加索裔和 30%~50%的亚裔肺癌患者检测出 EGFR 突变,而东亚不吸烟的肺癌患者检出率高达 50%~60%^[5]。

表皮生长因子受体酪氨酸激酶抑制剂(EGFR-

tyrosine kinase inhibitors, EGFR-TKI)通过与ATP竞争性结合酪氨酸激酶,阻断下游信号的激活,通过抑制细胞的增殖、分化、迁移及血管生成,上调Bcl-2蛋白家族促使细胞凋亡^[6]及增强自噬^[7]等途径达到抗肿瘤作用。

现EGFR-TKI已上市三代,第四代也处于临床研究阶段。第一代阿斯利康公司的吉非替尼(Gefitinib, Iressa)、罗氏公司的特罗凯(Erlotinib, Tarceva)和中国贝达公司的埃克替尼(Icotinib, Conmana)。第二代为勃林格殷格翰公司的阿法替尼(Afatinib, Gilotrif)和辉瑞公司的达克替尼(Dacomitinib)。第三代为阿斯利康公司的奥希替尼(Osimertinib, Tagrisso)。以下将详细介绍这些药物在晚期NSCLC中所开展的临床研究。

1 第一代 EGFR-TKI

第一代EGFR-TKI与酪氨酸激酶的结合是可逆的。

1.1 二三线治疗

2001年开展的IDEAL1&2研究^[8]证明Gefitinib可作为化疗失败晚期NSCLC患者的选择,不良反应可以耐受,250mg为最佳剂量。2002年和2003年其相继在日本、美国及澳大利亚上市,获准三线治疗晚期NSCLC^[9]。但随后的ISEL研究^[10]中总生存期(overall survival, OS)未见改善,2005年美国食品药品监督管理局(food and drug administration, FDA)只允许已经受益的患者使用。Ⅲ期INTEREST及V15-32研究中^[11]Gefitinib客观缓解率(objective response rate, ORR)较化疗组好,安全性及生活质量也更高,进一步奠定了其在晚期NSCLC二三线治疗的地位。

Erlotinib的BR21研究^[12]中无进展生存期(progression free survival, PFS)及OS均较安慰剂组有显著性差异。更大规模的TRUST^[13]及TITAN研究^[14]中Erlotinib的疾病控制率(disease control rate, DCR)达69%,亚裔患者达77%。因此,FDA于2004年批准其用于治疗至少一种化疗方案失败后的晚期NSCLC^[15]。

由于以上研究进行时间较早,当时未明确EGFR突变是疗效预测指标,仅发现亚裔、女性、不吸烟及腺癌的患者疗效好。

1.2 一线治疗

最著名的是Gefitinib的IPASS研究^[16]。它是一个证实EGFR突变的晚期NSCLC患者一线使用EGFR-TKI疗效较传统化疗(紫杉醇+卡铂)好。随后韩国开展的First-SIGNAL研究^[11]、日本进行的NEJ002^[17]及WJTOG3405研究^[18]、中国的OPTIMAL^[19]及CONVINCE研究、欧洲的EURTAC研究^[20]及亚洲的ENSURE研究^[21]进一步奠定了EGFR-TKI在突变患者一线治疗的地位。因此,FDA于2013年5月14日及2015年7月13日批准Erlotinib^[15]及Gefitinib^[9]用于EGFR外显子19缺失或21(L858R)取代突变的晚期NSCLC的一线治疗。

第一代EGFR-TKI较传统化疗给突变患者带来ORR及PFS突破性的进步,但中位PFS大约为8~14个月,之后会产生耐药,OS也未见延长^[22]。耐药机制如下^[23]:①“门卫”T790M突变:为最常见的耐药机制,占50%~60%,突变增加了ATP对酪氨酸激酶的亲和力,减弱了EGFR-TKI的结合;②下游信号通路的激活:如PI3K/AKT/mTOR通路,JAK2及STAT3通路等;③旁路激活:MET及HER2扩增、Her3过表达等;④组学转化:特别是上皮-间质转化或小细胞转化;⑤克隆异质性等。

第一代EGFR-TKI对常见突变(外显子19缺失或21 L858R取代突变)疗效好,对少见突变疗效欠佳。但随后深入的研究表明其对外显子20中A763-Y764insFQEA是有效的,ORR达86%,应予以重视^[24]。

2 第二代 EGFR-TKI

第二代EGFR-TKI与酪氨酸激酶结合是不可逆的;对T790M阳性、EGFR野生型及少见突变也有一定的疗效^[25]。

2.1 化疗及第一代EGFR-TKI耐药后治疗

I期临床研究发现Afatinib对第一代EGFR-TKI耐药有一定的疗效^[26]。由此深入的LUX-Lung1研究^[26]中Afatinib的ORR(7%)及PFS(3.3m)有统计学意义的改善,但OS未见差异且皮疹和腹泻等不良反应较安慰剂组高出10%,38%患者减量,18%患者停药;LUX-Lung4研究^[27]中ORR 8.2%,PFS 4.4m,OS 19.0m,但29%的患者停药。而Afatinib+cetuximab的方案ORR达29%,PFS 4.7m,但99%患者出现不

良事件,13%患者因严重的胃肠道和皮肤毒性而停药^[28]。与 Nimotuzumab 联合的研究^[29] ORR 达 23%, PFS 4.0m,但不良反应也较重。

Dacomitinib 的 ARCHER 1002 研究^[30]中 EGFR 突变患者的 ORR 仅为 8%。BR26 研究^[31]中 ORR(7%)及 PFS(2.66m)有改善,但总人群及 EGFR 突变人群的 OS 未有优势且不良反应多。

这些研究表明第二代 EGFR-TKI 对克服第一代 EGFR-TKI 耐药有着一定的疗效,尽管不尽如人意 (ORR<10%,PFS<5m)且未转化为生存的获益;Afinib+cetuximab/nimotuzuma 带来令人惊喜的 ORR,可能与对 EGFR 的双重抑制有关,但较高的不良反应发生率及医疗费用给临床上使用带来阻碍;是否与序贯使用二代 EGFR-TKI 有关,第二代 EGFR-TKI 因不良反应导致减量停药的比例较大,需予以注意。

2.2 一线治疗

Afinib 的 LUX-Lung3^[31]及 LUX-Lung6 研究^[33]再次证明了 EGFR-TKI 在突变患者一线治疗的地位。因此,美国、欧盟等国家批准 Afinib 一线治疗 EGFR 外显子 19 缺失或 21 取代突变的晚期 NSCLC^[34]。但两项研究的 PFS 均为 11 月余,未优于第一代 EGFR-TKI。OS 也未见延长。汇总分析后发现 19 缺失突变的患者 Afinib 组 OS 优于化疗组 (31.7m vs 20.7m, $P=0.0001$)^[35]。

Dacomitinib 的 ARCHER 1017 研究^[36]中 EGFR 突变患者 ORR 达 75.6%,PFS 18.2m,OS 40.2m。Ⅲ期 ARCHER 1050 研究^[37]美国临床肿瘤学会(American Society of Clinical Oncology,ASCO)最新数据显示 Dacomitinib 组 PFS 为 14.7m,略优于第一代 EGFR-TKI。

2.3 与第一代 EGFR-TKI 比较

LUX-Lung7 研究^[38]中 Afinib 的 ORR 及 PFS 略优于 Gefitinib。2017 年欧洲肺癌大会(European Lung Cancer Conference,ELCC)报道 Afinib 组进展后续用第三代 EGFR-TKI 的 OS 较 Gefitinib 组明显改善 (NE vs 48.3m)^[39]。Afinib 不良反应侧重于腹泻及皮疹,Gefitinib 则侧重于肝功能损害与间质性肺炎^[40]。LUX-Lung8 研究^[41]中 Afinib 的 DCR、PFS 及 OS 皆优于 Erlotinib。

ARCHER1028^[42]研究中 Dacomitinib 较 Erlotinib ORR 有改善。ARCHER1009^[42]研究中两组 PFS 均为 2.6m。对两研究 EGFR 突变患者进行汇总分析 OS

也未见差异且 Dacomitinib 不良反应较大^[43]。ARCHER 1050 研究^[37]中虽 Dacomitinib 组 PFS 显著延长,但减量比例高(66.1% vs 8%)且生活质量评分也未见改善。

由一二线研究结果可看出,第二代 EGFR-TKI 疗效略优于第一代 EGFR-TKI,特别是有延长长期生存率的趋势^[45]。肺鳞癌的二线治疗及 19 缺失突变的一线治疗可优先考虑 Afinib。第二代 EGFR-TKI 需特别注意不良反应的处理。

2.4 针对 EGFR 野生型和 T790M 阳性

Afinib 没有明显改善 EGFR 野生型患者的 PFS^[26]。Dacomitinib 的 ARCHER 1017^[36]中 EGFR 野生型患者 ORR、PFS 及 OS 分别为 7.1%、2.1m 及 19.7m,与第一代 EGFR-TKI 相似。

Afinib 的 I 期临床研究中 1 例 T790M 阳性患者疗效稳定^[26]。LUX-Lung4 研究^[27]中 1 例患者稳定 9 个月,1 例维持了 1 个月。而 Afinib+cetuximab 研究中^[28] T790M 阳性患者的 ORR 达 32%,PFS 4.8m。Dacomitinib 的 I 期临床研究中 T790M 阳性患者的 DCR 达 50%^[46]。而 II 期的 ARCHER 1002 研究^[30]中 Dacomitinib 治疗无效。

体外研究表明第二代 EGFR-TKI 能抑制 790M 阳性及 EGFR 野生型的活性,但临床效果欠佳,可能是由于起效所需药物剂量较大,远超过临床可实现的剂量,不良反应无法耐受^[25]。

2.5 针对 KRAS 野生型

Dacomitinib 对 KRAS 野生型患者有一定的疗效。I/II 期研究^[47]中 ORR 为 16.4%。BR26 研究^[31]中 PFS(3.1m)及 OS(7.0m)较安慰剂有统计意义的延长。ARCHER1028^[42]研究中 PFS 优于 Erlotinib ($P=0.006$)。故晚期 KRAS 野生型 NSCLC 患者多程治疗后考虑予以 Dacomitinib 实验性治疗。

2.6 针对少见突变

LUX-lung 2,3 和 6 研究的汇总分析表明 Afinib 对部分少见突变有着一定的疗效:G719X 的 ORR 为 78%,S768I 为 100%,L861Q 为 56%,这对少见突变临床决策的制定提供了一定的帮助^[48]。

3 第三代 EGFR-TKI

通过 C797 共价键不可逆地结合 EGFR 突变和

EGFR 突变/T790M,对 ErbB 家族的其他信号通路也有一定的抑制作用^[49]。

3.1 第一二代 EGFR-TKI T790M 阳性耐药

AURA I 期研究^[50]剂量爬升部分没有观察到剂量限制性毒性。剂量扩展部分 T790M 阳性患者 ORR 61%,DCR 95%,PFS 9.6m。80mg 为 Osimertinib 的最佳剂量。AURA II 期^[51]的 ORR 为 62%,DCR 90%,PFS 12.3m。AURA2 研究^[52]的 ORR 为 70%。AURA3 研究^[53]中 Osimertinib 的 ORR 及 PFS 均较化疗组改善(71% vs 31%,10.1m vs 4.4m, $P<0.001$)且不良反应轻。因此,2015 年 11 月 13 日 Osimertinib 获 FDA 批准治疗 EGFR-TKI 后进展 T790M 突变阳性的晚期 NSCLC^[54]。

3.2 一线治疗

AURA I 期 80/160mg 的扩展研究^[55]中总体 ORR 77%,DCR 97%,PFS 19.3m。而与 Gefitinib/ Erlotinib 相较的 FLAURA 研究在今年的欧洲肿瘤内科学会大会(European Society for Medical Oncology, ESMO)会议上公布了结果:ORR 80%,PFS 18.9m,优于第一二代 EGFR-TKI。

3.3 T790M 阴性

AURA I 期研究^[50]中组织 T790M 检测为阴性患者的 ORR 为 21%;AUAR 研究中血液及组织 T790M 检测均为阴性患者的 ORR 为 25%,PFS 2.8m^[56],是何原因需进一步的研究。

3.4 耐 药

第三代 EGFR-TKI 不可避免也面临着耐药问题。外显子 20 中的点突变 C797S 是最常见的耐药机制^[57],其他有 RAS/RAF/MEK 路径活化,MET、HER2 及 FGFR1 扩增,PIK3CA E545K 突变,上皮间质转化(EMT)和小细胞转化等^[58]。针对 C797S 的第四代 EGFR-TKI EAI045 正处于研究阶段^[59]。第一代和第三代 EGFR-TKI 的组合对 T790M 及 C797S 突变在不同等位基因上(反式)是有效的^[57]。间变性淋巴瘤激酶(anaplastic lymphoma kinase,ALK)抑制剂 Brigatinib 和 cetuximab 联合在克服 C797S 耐药方面表现出一定的疗效^[60]。Osimertinib 联合免疫抑制剂 Durvalumab 的 TATTON^[61]和 CAURAL 研究因较高的间质性肺病发生率而暂停。与 MET 抑制剂联用的研究(NCT02143466),与 Bcl-2 抑制剂 Navitoclax 联用的研究(NCT02520778)正在进行中,期待进一步的研究结果。

4 展 望

现 EGFR-TKI 在市场上出现了三代五个药,Dacomitinib 也准备上市。广大医生及患者面临着是 1+3/2+3/直接 3 代的抉择,FLAURA 结果的公布,将为我们选择指引方向。今年 ASCO 上吴一龙的 ADJUVANT(CTONG1104)研究将 EGFR-TKI 的使用扩展到了术后辅助治疗领域,并取得了令人惊喜的结果;Gefitinib 组延长无病生存期(disease free survival, DFS)(28.7m vs 18.0m),肿瘤复发风险下降 40%。Osimertinib 的 ADAURA 研究也正在进行。它们将为 EGFR-TKI 打开新的大门。

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