

CDK4/6 抑制剂在乳腺癌中的研究进展

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摘 要:细胞周期的失调是肿瘤生长和转移的典型标志之一,通过 CDK 抑制剂重新建立细胞周期的调控在肿瘤靶向治疗的发展中已经成为有吸引力的方向。三种选择性靶向 CDK4/6 的口服药物已经被研发:palbociclib,abemaciclib 和 LEE011。当前的研究表明 CDK4/6 抑制剂与内分泌药物联合治疗激素受体阳性乳腺癌是一个新的标准。全文就细胞周期调控、乳腺癌中 cyclinD-CDK4/6-Rb 途径及相关蛋白 p16 和 survivin 的异常表现、CDK4/6 抑制剂的相关临床试验及其结果进行总结。

关键词:乳腺癌;HR+;CDK4/6 抑制剂;survivin;p16

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Research Progress of Application of CDK4/6 Inhibitors in Breast Cancer

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Abstract: Dysregulation of cell cycle is one of the typical signs of tumor growth and metastasis, re-establishing cell cycle control through CDK inhibitors has become an attractive direction in the development of targeted cancer therapy. Three oral agents selectively targeting CDK4/6 have been developed: palbociclib, abemaciclib and LEE011. Current researches indicate that CDK4/6 inhibitors combined with endocrine therapy is a new therapeutic approach for hormone receptor-positive breast cancer. The cell cycle regulation, abnormalities of cyclinD-CDK4/6-Rb pathway and the related p16 and survivin in breast cancer and the results of CDK4/6 inhibitors in clinical trials are summarized in this article.

Key words: breast cancer; HR+; CDK4/6 inhibitors; survivin; p16

乳腺癌是当今中国女性最常见的癌症^[1],在全球新确诊的乳腺癌病例中,中国占 12.2%^[2]。HR+乳腺癌约占所有类型乳腺癌的 3/4^[3],内分泌治疗是这类乳腺癌的有效治疗方式之一,然而内分泌治疗耐药是当前临床面临的巨大挑战。阐明内分泌治疗耐药的机制从而开创更有效的疗法是目前研究的当务之急。目前已知的内分泌耐药机制与 ER 的结构和功能异常、ESR1 基因突变、多种生长因子信号通路的异常激活、miRNA 表达的改变、内分泌药物的代谢、细胞周期的失控等因素相关。为提高 HR+乳腺癌内分泌治疗的疗效,多种靶向新药正在研发和试验中。对于 HR+晚期乳腺癌的临床研究,最近最成

功的例子是使用 CDK4/6 抑制剂 palbociclib 与芳香化酶抑制剂联合治疗雌激素受体阳性乳腺癌。

1 细胞周期调控

正常细胞的增殖是受到严格调控的,这一过程的失调会导致细胞无限制的生长和增殖,是很多癌症包括乳腺癌的主要标志之一。典型的细胞周期各阶段分为:G₀(静止期)、G₁(DNA 合成前期)、S(DNA 合成期)、G₂(分裂前期)和 M(细胞分裂期)。在细胞周期运转调控中,细胞周期蛋白(cyclin)和周期蛋白依赖性激酶(CDKs)发挥了非常重要的作用,细胞周期是由 cyclin 和 CDKs 之间的相互作用所驱动^[4]。从 G₁期到 S 期是细胞正常复制的关键时期,在这一过程

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中,cyclinD-CDK4/6-Rb起着重要作用。cyclinD与CDK4/6结合形成cyclinD-CDK4/6复合物,使Rb蛋白磷酸化,进而释放E2F促使细胞周期从G₁期转换到S期。细胞周期中CDKs的水平通常是不变的,他们的活性是受细胞周期蛋白在各细胞周期的水平控制。由于CDKs在细胞增殖中的作用,其可作为抗癌治疗的天然靶标。因此,在肿瘤靶向治疗的发展中,通过CDK抑制剂重新建立对细胞周期的控制一直是一个有吸引力的方向^[5]。

2 乳腺癌中 cyclinD-CDK4/6-Rb 的异常表现

通过扰乱cyclinD-CDK4/6-Rb途径来促进细胞增殖,其中可能的机制包括:①cyclinD过表达或扩增,在15%~20%人类乳腺癌中有cyclinD1基因(CCND1)的扩增,而蛋白过表达比基因扩增更普遍,cyclinD1过表达高达50%^[6,7];②CDK4/6基因突变和扩增,15%的乳腺癌CDK4基因有扩增,导致CDK4蛋白过表达^[8];③调节cyclinD与CDK4/6结合抑制剂的丢失,如INK4蛋白(p16^{INK4A}、p15^{INK4B}、p18^{INK4C}、p19^{INK4D}),尤其p16丢失是在乳腺癌组织中最常见的异常之一^[9];④Rb的丢失或突变,20%~30%的乳腺癌特别是三阴性乳腺癌有Rb基因缺失或突变,但大多数乳腺癌中Rb的失活是由于cyclinD1的过表达或p16的失活导致^[5,10,11]。

很多乳腺癌表现出cyclinD-CDK4/6-Rb的失调,cyclinD1-CDK4/6的过度活化又常见于ER+乳腺癌^[12]。有研究表示,对ER+乳腺癌的抗雌激素治疗可能是通过减少cyclinD1表达和活性及后续的Rb磷酸化实现的^[13],内分泌耐药可能和cyclinD1过表达和Rb磷酸化有关^[14]。cyclinD1和雌激素刺激ER应答基因的转录,表现为协同作用,另外,cyclinD1被证明在雌激素缺乏的条件下能表现出激活ER的能力^[15],这为CDK4/6抑制剂克服内分泌耐药的治疗提供了可能的理论基础。但同时也有研究显示cyclinD1的表达与ER、Her-2显著相关,cyclinD1的表达与ER表达呈正相关,与Her-2表达呈负相关,cyclinD1的阳性表达预示着较好的预后^[16]。基于cyclinD-CDK4/6-Rb途径在癌症发展中重要角色及其在乳腺癌中的常见异常改变,为针对这一途径组

成元件的靶向治疗提供了有力的理论根据,特别是对于ER+乳腺癌。

3 与 CDK4/6 结合的 p16、survivin 蛋白异常表现

INK4(inhibitor of CDK4)是细胞周期素依赖性激酶抑制物(CDI)的一类,而p16蛋白是INK4家族成员之一,p16蛋白是作用于CDK4的抑制因子,p16蛋白抑制CDK4活性,最终阻止细胞进入S期,抑制肿瘤发生发展。另外,近年研究表明是survivin蛋白是最小的凋亡抑制蛋白IAP基因家族重要成员之一,与肿瘤的发生、发展密切相关。下调survivin能够增强TAM介导的细胞凋亡,相反,survivin基因转染的MCF-7细胞表现出较低的凋亡率,结果表明survivin是影响他莫昔芬诱导的乳腺癌细胞凋亡和对其产生耐药的一个重要因子^[17]。与正常组织相比,survivin蛋白在分裂细胞如肿瘤细胞中高表达,因此survivin与细胞周期进展相关,在抑制细胞凋亡和调节细胞分裂方面起着关键作用,survivin还诱导血管生成,在有丝分裂过程中通过激活多个信号通路维护肿瘤生长^[18,19]。除此之外,有研究显示在survivin过表达的细胞中,S期和G₂/M期总数增加,而当survivin功能失活,磷酸化的Rb、CDK2/cyclinE复合物及S期数量均减少^[20]。survivin与CDK4结合,可竞争性地使p16与CDK4分离,形成survivin/CDK4复合物,将CDK4运送至细胞核,因cyclinD1与CDK4的相互结合力比survivin与CDK4的结合力更强,从而被cyclinD1/CDK4复合物取代,导致Rb磷酸化,进而使细胞从G₁期向S期转换^[20]。

4 CDK4/6 抑制剂

4.1 palbociclib

Palbociclib能够与CDK4/6蛋白的ATP结合位点相结合发挥抑制作用,抑制Rb磷酸化,进而抑制转录因子E2F的释放,来阻止细胞由G₁期进入S期,从而抑制DNA的合成及细胞增殖,而不表现出泛CDK抑制剂的严重细胞毒性。Finn等^[12]评价了在体外不同分子特性的人类乳腺癌细胞对CDK4/6抑制剂palbociclib的反应敏感性,结果其对Luminal

ER+细胞系的抑制作用最为明显,在ER-或基底样亚型中作用最小;在ER+细胞系观察到CDK4/6抑制剂与他莫昔芬有协同作用。CDK4/6抑制剂palbociclib联合内分泌治疗的PALOMA-1、PALOMA-2和PALOMA-3系列研究:PALOMA-1研究是一个临床2期研究,比较来曲唑联合或不联合CDK4/6抑制剂药物palbociclib在ER+/Her2-绝经后不适合手术的转移或局部复发乳腺癌患者一线治疗中的作用,研究纳入了165例患者,结果显示,与来曲唑单药相比,palbociclib联合来曲唑治疗将PFS从10.2个月提高到20.2个月。其副作用也在可控范围内^[21]。基于这项研究结果,2015年2月,FDA授权palbociclib为加速研发药物,与来曲唑联合用于绝经后ER+/Her2-的转移性乳腺癌的治疗。PALOMA-2研究类似于PALOMA-1研究,两者不同之处在于:PALOMA-2是一项双盲研究,被纳入的650例患者随机分组,接受palbociclib联合来曲唑和来曲唑联合安慰剂治疗,结果显示联合组PFS从9个月提高到14个月^[22]。PALOMA-3研究是一个临床3期研究,比较palbociclib联合氟维司群和氟维司群联合安慰剂治疗晚期HR+/Her2-乳腺癌患者的疗效,纳入的521例患者为前线内分泌治疗失败的患者。这项研究被终止的时间比预期的早,因为研究的主要终点PFS已经被观察到,结果显示,palbociclib联合氟维司群同氟维司群联合安慰剂比较,PFS从3.8个月提高到9.2个月^[23]。现有的临床研究数据表明CDK4/6抑制剂在乳腺癌的治疗中展现出不错的疗效并具有巨大的潜力。

4.2 LY2835219(abemaciclib)

Abemaciclib是另一种高度特异的口服小分子CDK4/6抑制剂,抑制Rb磷酸化,导致G₁期阻滞,从而抑制细胞增殖。临床前数据展示出abemaciclib在多种肿瘤中作为单药或与化疗相结合的抗肿瘤活性作用,另外,abemaciclib能通过血脑屏障抑制颅内肿瘤的生长^[24-26]。MONARCH 1是一项有关abemaciclib单药治疗的II期临床研究,纳入了132例经内分泌及化疗治疗后进展的HR+/Her2-转移性乳腺癌患者。2016年6月ASCO会议上对该研究进行了口头报告,临床数据的最终分析显示,总缓解率(ORR)为19.7%,临床获益率(患者获得CR、PR或SD时间为6个月及以上)为42.4%,中位无进展生

存期(PFS)为6个月。MONARCH1研究的数据表明abemaciclib这一CDK4/6抑制剂能够有效抑制肿瘤生长,延长患者的生存时间,且耐受性较好。目前正在进行的与内分泌药物联合的相关临床研究:MONARCH-2双盲、3期研究(n=630),比较abemaciclib联合氟维司群与安慰剂加氟维司群在绝经后HR+/Her2-局部晚期或转移性乳腺癌中的治疗效果^[27]。MONARCH-3研究(n=450)比较abemaciclib联合阿那曲唑或来曲唑与安慰剂加阿那曲唑或来曲唑治疗没有接受全身治疗的HR+/Her2-局部区域复发或转移性乳腺癌的疗效。PFS均是主要观察结果^[28],相关结果拭目以待。

4.3 LEE011(ribociclib)

LEE011与palbociclib类似,也为口服小分子CDK4/6抑制剂。在体外实验模型中LEE001导致G₁期阻滞,表现出抗肿瘤活性作用,包括有BRAF或NRAS基因突变的恶性黑色素瘤及乳腺癌^[29]。目前正在进行的多项临床试验将为LEE011的肿瘤治疗提供更多的依据。LEE011对于HR+/Her2-乳腺癌的相关临床研究见附录。

5 总结与展望

大量数据证明CDK4/6和cyclinD1在细胞周期调控中的重要作用,同时临床数据表明CDK4/6抑制剂对乳腺癌生长有抑制作用,特别是对HR+乳腺癌疗效显著。目前CDK4/6抑制剂的抗肿瘤治疗已经取得一定进展,CDK4/6抑制剂如何与其他化疗及靶向药物理想组合将是一个重要临床问题。对于Her-2阳性乳腺癌主要治疗手段是化疗联合分子靶向药物,如曲妥珠单抗、帕妥珠单抗、拉帕替尼及TDM-1等。相关临床前研究表明Her-2阳性乳腺癌细胞株对CDK4/6抑制剂也有较高敏感性^[12],CDK4/6抑制剂可能同样使Her-2阳性乳腺癌患者受益,对此,还需更多的临床研究来证实其确切疗效。CDK4/6抑制剂与化疗药物联合治疗的疗效有待进一步探究,特别对于ER、PR和Her-2均阴性的三阴性乳腺癌,化疗是其主要治疗手段,目前还没有证据表明三阴性乳腺癌患者能从联合CDK4/6抑制剂的治疗中获益。CDK4/6抑制剂与化疗药物如卡培他滨及mTOR抑制剂依维莫司等联合治疗的众多临床

研究也正在进行中。到目前为止,除 ER 外,没有其他生物标志物帮助预测哪些患者能够受益于 CDK4/6 抑制剂的治疗,所以寻找潜在可能的生物标志物,筛选获益人群,将有助于实现个体化精准治疗。另外,CDK4/6 突变与 CDK4/6 抑制剂的疗效及耐药的关系有待进一步认识和研究,对 CDK4/6 抑制剂原发或继发耐药后其机制的进一步研究将可能作为未来一个重要方向。

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附录 LEE011 对于 HR+/Her-2-乳腺癌的相关临床研究

临床试验	治 疗	研究人群	阶段	主要终点	参考文献
NCT01857193	LEE011+依西美坦+依维莫司和 LEE011+依西美坦 vs 依西美坦+依维莫司	阿那曲唑或来曲唑治疗失败的绝经后 HR+、HER2-局部晚期或转移性乳腺癌	1b/2 (N=185)	PFS, 剂量限制性毒性	[30]
MONALEESA-2 NCT01958021	LEE011+来曲唑 vs 安慰剂+来曲唑	先前未经治疗的绝经后 HR+、HER2-局部复发或转移性乳腺癌, 也接受曾新辅助或辅助治疗, 若治疗中包括来曲唑或阿那曲唑, 需完成治疗后无疾病间隔时间至少 12 个月	3 (N=650)	PFS	[31]
MONALEESA-7 NCT02278120	LEE011+他莫昔芬或+来曲唑/阿那曲唑+戈舍瑞林 vs 安慰剂+他莫昔芬或+来曲唑/阿那曲唑+戈舍瑞林	未接受内分泌治疗绝经前或围绝经期年龄 18 岁到 59 岁之间的 HR+、HER2-局部复发或转移性乳腺癌	3 (N=660)	PFS	[32]
NCT02088684	LEE011+buparlisib(BKM120)+氟维司群 vs LEE011+BYL719(PI3K α 抑制剂)+氟维司群 vs LEE011+氟维司群	内分泌治疗和/或化疗后绝经后 HR+、HER2-局部复发或转移性乳腺癌	1b/2 (N=216)	PFS (2 阶段), 剂量限制性毒性 (1b 阶段)	[33]