CDK4/6抑制剂耐药乳腺癌处理策略及其机制研究进展

马嘉忆,殷文瑾,吴子平,陆劲松*

上海交通大学医学院附属仁济医院乳腺外科,上海 200127

摘要 概述了CDK4/6抑制剂耐药乳腺癌的治疗策略,分析了CDK4/6抑制剂跨线治疗、新型口服SERDs药物、PI3K/AKT/mTOR抑制剂、ADC类药物、AURKA抑制剂、HDAC抑制剂、免疫治疗和抗衰老药物在CDK4/6抑制剂进展后的临床研究结果及其相关机制。展望未来,可开展更多临床研究的潜在靶点。

关键词 细胞周期蛋白依赖性激酶4/6抑制剂;晚期乳腺癌;耐药机制;内分泌治疗

细胞周期中每个间期的过渡需要细胞周期蛋白(cyclin)和对应的细胞周期蛋白依赖性激酶(cyclin-dependent kinase,CDK)结合从而推动进程[1]。正常细胞周期蛋白及其激酶的活性受到雌激素受体(estrogen receptor,ER)等细胞核受体、人表皮生长因子受体2(human epidermal growth factor receptor 2,HER2)等细胞膜受体、磷脂酰肌醇-3激酶(phosphatidylinositol-3 kinase,PI3K)/丝氨酸-苏氨酸蛋白激酶(serine/threonine kinase,AKT)/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)等胞内通路,以及靶向CDK4和CDK6的CDK4抑制剂(inhibitor of CDK4,INK4)p16、p15、p18、p19和靶向cyclin-CDK复合物的CDK相互作用蛋白/激酶抑制蛋白(CDK interacting protein/kinase inhibitor protein,CIP/KIP)p21、p27、p57等内源性CDK抑制剂(cyclin-dependent kinase inhibitor,CDKI)的调节。但在病理情况下,细胞周期会因为异常信号的调控而导致细胞过度增殖,由此启发采用外源性CDKI以抑制肿瘤细胞增殖的治疗理念[2]。

细胞周期蛋白依赖性激酶4/6(cyclin-dependent kinase 4/6,CDK4/6)抑制剂的首要作用是阻滞细胞周期从而抑制细胞增殖过程,药物通过与CDK4和CDK6的三磷酸腺苷(adenosine triphosphate,ATP)结合位点结合,使ATP的磷酸基团无法传递给下游的视网膜母细胞瘤(retinoblastoma,Rb)蛋白,导致Rb蛋白无法通过磷酸化释放转录因子E2F进而阻断其转录下游基因,从而下调cyclin

收稿日期:2023-05-26;修回日期:2023-06-25

基金项目:北京医学奖励基金会项目(YXJL-2020-0941-0737)

作者简介:马嘉忆,博士研究生,研究方向为乳腺癌内分泌治疗耐药机制及其应对策略,电子信箱:longestma@163.com;陆劲松(通信作者),主任医师,研究方向为乳腺癌的临床与基础,电子信箱:lujingsong@renji.com

引用格式:马嘉忆, 殷文瑾, 吴子平, 等. CDK4/6抑制剂耐药乳腺癌处理策略及其机制研究进展[J]. 科技导报, 2023, 41(18): 58-66; doi: 10.3981/j.issn.1000-7857.2023.18.008

D1-CDK4/6-Rb通路的表达,使细胞周期停滞在DNA合成前期(G1期),阻遏细胞分裂[3-5]。CDK4/6抑制剂联合内分泌治疗在激素受体(hormone receptor,HR)阳性/HER2阴性进展期乳腺癌(advanced breast cancer,ABC)的治疗已被《晚期乳腺癌国际共识指南》(第五版)和美国国际综合癌症网络发布的指南等推荐为标准治疗方案[6-7],然而,即便在晚期一线就使用CDK4/6抑制剂,仍有一半的患者会在用药2年左右出现疾病进展[8-12]。因此,本研究对CDK4/6抑制剂耐药的治疗策略以及机制等相关研究进展作一综述。

1　CDK4/6抑制剂耐药的治疗策略

CDK4/6抑制剂耐药的治疗策略目前有多种选择,可考虑以下几类:CDK4/6抑制剂跨线治疗、新型选择性雌激素受体降解剂(selective estrogen receptor degraders,SERDs)、CDK4/6抑制剂耐药通路相关的靶向药物、组蛋白去乙酰化酶(histone deacetylase,HDAC)抑制剂、免疫治疗、抗衰老药物。

1.1　CDK4/6抑制剂跨线治疗

多项研究显示,CDK4/6抑制剂治疗进展后,患者可以继续从序贯其他内分泌治疗药物联合相同或者不同的CDK4/6抑制剂中获益[13-15]。Wander等[14]在哌柏西利治疗进展的HR+/HER2-转移性乳腺癌(metastatic breast cancer,MBC)患者中探索了序贯阿贝西利的疗效,结果发现中位无进展生存期(progression-free survival,PFS)为5.3月。Martin等进行的真实世界研究发现,与CDK4/6抑制剂进展后接受化疗相比,继续CDK4/6抑制剂治疗者的PFS(P<0.0001)和总生存期(overall survival,OS;P<0.00001)更长[15]。II期随机临床试验MAINTAIN研究纳入了119例CDK4/6抑制剂一线治疗后进展的HR+/HER2-MBC患者,1∶1分配至瑞波西利联合内分泌治疗组和安慰剂联合内分泌治疗组,结果发现瑞波西利组比安慰剂组取得了显著的PFS获益(中位PFS:5.29月相比2.76月,P=0.006)[16]。

CDK4/6抑制剂治疗进展也可能与其联用的芳香化酶抑制剂(aromatase inhibitor,AI)耐药有关,*ESR1*突变是患者在接受AI这一雌激素剥夺治疗后出现获得性耐药的常见原因。SERDs通过直接抑制*ER*基因转录达到抑制乳腺肿瘤生长的作用,对*ESR1*突变的肿瘤也有治疗作用[17]。目前常用的SERDs为氟维司群,不仅抑制ER向细胞核移位,还可以增加ER泛素化降解[18]。III期随机临床试验PADA-1通过监测患者接受哌柏西利联合AI治疗过程中循环肿瘤DNA(circulating tumor DNA,ctDNA)里*ESR1*是否有新出现或较前增加的突变,在这类患者中比较了将方案调整为氟维司群联合哌柏西利和继续AI联合哌柏西利治疗的PFS差异,结果发现转换为氟维司群患者的中位PFS相比继续AI治疗的患者延长了6.2月(11.9月相比5.7月,P=0.004)[19]。

由此可见,CDK4/6抑制剂进展后依据患者的不同情况,更换所联用的内分泌治疗药物同时维持原CDK4/6抑制剂或更换为另一种CDK4/6抑制剂都是可选择的方案。

1.2　新型单药SERDs

艾拉司群(elacestrant)作为新一代口服SERDs能够选择性结合ER并诱导其降解[18],是CDK4/6抑制剂治疗进展患者的选择之一。III期随机临床试验EMERALD研究在477例接受过一或二线内分泌治疗且既往CDK4/6抑制剂联合氟维司群或AI后进展的ER+/HER2-ABC患者中探索艾拉司群和标准内分泌治疗(氟维司群或AI)的疗效差异,结果发现艾拉司群相较于标准内分泌治疗带来了显著的PFS获益(12个月PFS率:22.3%相比9.4%,P=0.002),*ESR1*突变的患者也能从艾拉司群治疗中显著获益(12个月PFS率:26.8%相比8.2%,P=0.0005)[20]。

尽管艾拉司群一定程度上改善了CDK4/6抑制剂耐药问题,但其他新型SERD类药物的研究结果目前并不尽如人意。吉雷司群(giredestrant)是一种新型口服选择性ER拮抗剂和降解剂,临床前研究显示其单药或联合CDK4/6抑制剂在*ESR1*突变或野生型的人源肿瘤异种移植模型中呈现出显著的抗肿瘤作用[21],然而在2022年欧洲医学肿瘤学会

公布的结果中,其Ⅱ期临床试验acelERA BC研究显示,对于接受过至少2线治疗(需包含内分泌治疗)的ER+/HER2-ABC患者,吉雷司群相比医生选择的内分泌治疗(氟维司群或芳香化酶抑制剂)并未能显著改善PFS(5.6月相比5.4月,*P*=0.176),*ESR*1基因突变亚组中,似乎相比医生选择的内分泌治疗组,吉雷司群组的PFS倾向于更长(5.3月相比3.5月,*P*=0.061)[22]。另一新型SERD药物amcenestrant在其Ⅱ期临床试验AMEERA-3研究中也未能达到理想的疗效,amcenestrant单药组和医生选择的治疗组治疗ER+/HER2-ABC的PFS相近(3.6月相比3.7月,*P*=0.643),而在*ESR*1突变亚组中,amcenestrant组可能有一定优势[PFS:3.7月相比2.0月,95%置信区间(CI):0.595~1.403][23]。

新型口服SERD类药物是否能够改善CDK4/6抑制剂耐药问题还有待研究,目前来看,*ESR*1突变人群可能从这类药物中取得更显著的获益。

1.3 CDK4/6抑制剂耐药通路相关靶点

1.3.1 PI3K/AKT/mTOR抑制剂

PI3K/AKT/mTOR通路在肿瘤中有促进细胞增殖和抵抗凋亡的作用,高达41%~48%的ER+乳腺癌存在PI3K/AKT/mTOR通路相关基因的改变,最常见的是*PIK3CA*突变,部分还有*AKT*突变和*PTEN*缺失[24-25]。Abu-Khalaf等[26]研究发现,CDK4/6抑制剂治疗后,疾病进展患者的肿瘤细胞和周围基质/免疫细胞中的PI3K/AKT/mTOR通路被激活,而使用mTOR抑制剂和CDK4/6抑制剂双靶治疗ER+乳腺癌后,E2F的转录功能受到了显著抑制[27]。此外,PI3K/mTOR抑制剂还可以通过降低CDK4/cyclin D1表达水平恢复细胞对哌柏西利的敏感性[28]。由此可见,PI3K/AKT/mTOR通路的抑制剂或可成为逆转CDK4/6抑制剂治疗耐药的方式之一[29]。因此,探索验证CDK4/6抑制剂进展后应用PI3K/ATK/mTOR抑制剂疗效的临床研究应运而生。

SOLAR-1研究中采用的PI3Kα抑制剂阿培利司(alpelisib)联合氟维司群治疗为伴有PIK3CA突变的HR+/HER2-ABC患者带来了11.0个月的中位PFS获益,其中5.9%的患者接受过CDK4/6抑制剂[30]。随后BYLieve在CDK4/6抑制剂联合AI后进展的HR+/HER2-且伴有PIK3CA突变的ABC患者中再次验证了阿培利司联合内分泌治疗可为50.4%的患者带来至少6个月的PFS[31]。CAPItello-291研究在HR+/HER2-ABC绝经后女性或男性患者中证实了*AKT*抑制剂卡匹色替(capivasertib)+氟维司群组的中位PFS是氟维司群单药组的2倍(7.2月相比3.6月,*P*<0.001),其中69.1%的患者接受过CDK4/6抑制剂[32],在CDK4/6抑制剂经治亚组中,卡匹色替相比安慰剂组能够延长2.9月的中位PFS(5.5月相比2.6月,95%CI:0.48~0.72),且无论CDK4/6抑制剂治疗持续时间<12个月或≥12个月,卡匹色替相比安慰剂都能使PFS得到延长[32]。TRINITI-1研究则是在104例HR+/HER2-ABC患者(其中96例接受过CDK4/6抑制剂)中采用瑞波西利联合mTOR抑制剂依维莫司和依西美坦治疗,在95例CDK4/6抑制剂治疗后疾病进展且可评估疗效的患者中临床获益率达到41.1%[33]。

1.3.2 抗体药物偶联物

德曲妥珠单抗(trastuzumab deruxtecan,T-DXd)是一种以8∶1药物抗体比连接曲妥珠单抗和拓扑异构酶Ⅰ抑制剂的新型抗体药物偶联物(antibody drug conjugate,ADC)药物。基础研究发现HER2与ER通路存在交互作用[34-35]。Viganò等[36]发现受体酪氨酸激酶(receptor tyrosine kinase,RTK)功能的激活可能是导致ER+/HER2低表达肿瘤耐药的原因之一。全外显子测序在59例CDK4/6抑制剂经治患者的肿瘤组织中发现HER2的突变或扩增可能与CDK4/6抑制剂耐药有关[37]。临床研究中,DESTINY-Breast04为T-DXd在HER2低表达ABC患者中的应用提供了依据。该研究纳入557例HER2低表达且接受过一或二线化疗的患者,其中88.7%为HR+且该亚组中逾70%的患者接受过CDK4/6抑制剂治疗。该研究比较了T-DXd和医生选择化疗的疗效和安全性,结果显示在HR+亚组中T-DXd可较医生选择的化疗方案显著延长PFS(中位PFS:10.1相比5.4个月,*P*<0.001)和OS(中位OS:23.9个月相比17.5个月,*P*=0.003)[38]。

戈沙妥珠单抗(sacituzumab govitecan,SG)是一种靶向人滋养细胞表面抗原2(Trophoblast Cell-

Surface Antigen 2,TROP-2)的ADC药物。乳腺癌的所有亚型中都广泛存在TROP-2的表达,研究发现93%的三阴性乳腺癌样本中存在TROP-2高表达,ER阳性乳腺癌中该比例约为50%[39-40]。一项I/II期单臂临床研究(NCT01631552)在54例转移阶段接受过至少一线解救化疗和一线解救内分泌治疗的HR+/HER2-MBC患者中研究了SG的疗效,其中59.3%的患者接受过CDK4/6抑制剂,中位随访11.5个月后客观缓解率(objective response rate,ORR)为31.5%[41]。III期临床研究TROPiCS-02试验纳入了543例晚期阶段接受过内分泌治疗、CDK4/6抑制剂和2-4线化疗的HR+/HER2-MBC患者,比较了SG和医生选择治疗的疗效,结果发现SG组的PFS显著优于医生选择治疗组(中位PFS:5.5个月相比4.0个月,P=0.0003)[42]。因此,对于CDK4/6抑制剂治疗失败的患者,SG是可考虑的后线治疗选择之一。

1.3.3　AURKA抑制剂

极光激酶A(aurora kinase A,AURKA)属于丝氨酸/苏氨酸激酶家族,通过cyclin B1-CDK1的磷酸化激活促进有丝分裂纺锤体组装并调节细胞周期从DNA合成后期(G2期)向细胞分裂期(M期)过渡[43]。在ER阳性乳腺癌中,AURKA可通过诱导上皮-间质转化促进肿瘤远处转移[44],体外实验证实其过表达还会导致CDK4/6抑制剂耐药[37]。全外显子测序结果显示接受过CDK4/6抑制剂患者的肿瘤组织中AURKA扩增与CDK4/6抑制剂耐药有关[37]。

阿立色替(alisertib)是一种AURKA抑制剂。II期随机临床试验TBCRC041研究纳入了96例既往接受过氟维司群的HER2-绝经后MBC患者,1∶1随机分配至阿立色替+氟维司群组和阿立色替单药组。91例可评估疗效的患者均接受过CDK4/6抑制剂治疗,结果发现2组的ORR分别为19.6%和20.0%[45],提示AURKA抑制剂阿立色替单药治疗对CDK4/6抑制剂耐药的患者可能有一定疗效。AURKA抑制剂后续相关研究值得继续关注。

1.4　HDAC抑制剂

表观遗传修饰会影响基因表达水平,HDAC抑制剂通过调控组蛋白乙酰化状态来发挥细胞周期阻滞、诱导分化、凋亡、自噬、衰老和抗肿瘤免疫的作用[46]。

ACE研究入组了365例至少一种内分泌治疗方案进展(辅助、新辅助或转移性)的HR+/HER2-绝经后ABC患者,结果发现HDAC抑制剂西达本胺联合依西美坦组可以达到7.4月的中位PFS,优于安慰剂联合依西美坦组的3.8月(P=0.033)[47],为西达本胺在ABC中的应用奠定了基础。一项调查CDK4/6抑制剂进展后序贯治疗方案的真实世界研究发现,200例HR+/HER2-MBC患者中有21例接受了西达本胺为基础的治疗,而该亚组获得了2.6个月的中位PFS[48]。另一项真实世界研究在44例CDK4/6抑制剂进展后接受过西达本胺治疗的HR+/HER2-MBC患者中发现,总人群患者的中位PFS仅2.0月,而其中CDK4/6抑制剂进展后即刻使用西达本胺治疗患者的中位PFS达到了4.5月[49]。因此,从数据上来看,CDK4/6抑制剂进展后立即使用西达本胺治疗可能疗效更佳,然而,患者的治疗线数、转移部位数量、既往治疗方案等因素也可能对结果造成影响,还需要前瞻性研究进一步探索。

1.5　免疫治疗

CDK4/6抑制剂治疗后程序性死亡受体-配体1(PD-L1)增高导致的免疫逃逸也是其耐药原因之一。耐药相关机制可能有以下2种:其一,CDK4/6抑制剂通过抑制cyclin D-CDK4介导的斑点型POZ蛋白(SPOP)磷酸化,使得PD-L1蛋白无法通过泛素化途径降解进而在胞内累积[50];其二,另有研究发现抑制CDK4/6后,癌基因*Myc*的蛋白表达增高[51],而*Myc*可以直接与PD-L1基因的启动子结合从而使PD-L1表达增高[52-53]。2种途径最终都会由于PD-L1高表达导致肿瘤细胞发生免疫逃逸。临床前研究中,CDK4/6抑制剂与PD-L1抑制剂呈现出协同抗肿瘤作用[50, 54],诱导抗原呈递增强,T细胞介导的免疫激活和细胞周期阻滞增强[54]。故CDK4/6抑制剂进展后的免疫监测点抑制剂治疗的临床疗效研究是目前重要的临床研究方向。

1.6　抗衰老药物

CDK4和CDK6受到抑制时,Rb1和转录因子叉头框蛋白质M1(forkhead box protein M1,

FOXM1)的抗衰老作用也会受到阻遏[55-56],细胞进入衰老状态,伴随衰老相关的分泌表型(senescence-associated secretory phenotype,SASP)发生变化。而SASP会促进肿瘤微环境发生血管重塑等变化,招募细胞毒性T细胞,增强肿瘤细胞表面的I类主要组织相容性复合体的表达,促进细胞毒性T细胞的活化,提高其肿瘤浸润和活性,起到重塑免疫微环境的作用[57-58]。然而衰老是把双刃剑,在阻滞细胞周期、抑制肿瘤增殖的同时,SASPs还会引起慢性炎症、白介素6(IL6)等因子介导的细胞干性和侵袭性增加,从而促进肿瘤发展[59]。

二甲双胍是抗衰老药物之一,主要抗衰作用是调节SASPs。有研究表明,二甲双胍在头颈鳞状细胞癌中通过抑制mTOR和信号转导和转录激活因子3(signal transduction and transcription activator 3,STAT3)通路可以调节CDK4/6抑制剂诱导的SASP,并阻断IL6-STAT3通路抑制细胞干性,从而提高CDK4/6抑制剂的疗效[60]。基于以上临床前研究,二甲双胍及其他抗衰老药物在乳腺癌CDK4/6抑制剂进展后是否能够提高后续治疗的疗效还有待深入临床探索。

2 其他耐药机制及潜在治疗策略

2.1 FGFR扩增和突变

成纤维细胞生长因子受体(fibroblast growth factor receptor,FGFR)在细胞增殖、分化和生长等多方面参与肿瘤发生发展。TCGA数据库显示FGFR1在15%的ER阳性乳腺癌患者中存在扩增和/或突变[61],在接受哌柏西利治疗后进展的34例ER+/HER2-乳腺癌患者治疗后的血浆ctDNA测序中,41%的患者检测到FGFR1和FGFR2存在扩增或突变[61]。Mao等[62]对60例ER阳性转移性乳腺癌(metastatic breast cancer,MBC)患者治疗前后的组织进行全外显子测序,发现40%的患者在接受内分泌治疗后出现FGFR1、FGFR2或FGF3扩增或FGFR2突变,并通过体外实验证实了FGFR/FGF的改变会引起氟维司群和CDK4/6抑制剂耐药,其作用机制主要是FGFR/FGF对ER重编程及丝裂原活化蛋白激酶(mitogen-activated protein kinases,MAPKs)的活化作用,加用FGFR抑制剂后耐药能够逆转。厄达替尼(erdafitinib)等FGFR抑制剂相关的临床研究目前还在进行中(NCT03238196等)。

2.2 Rb蛋白低表达和cyclinE1高表达

Rb蛋白是抑癌蛋白,Rb蛋白被CDK4/6磷酸化激活与E2F1转录因子分离,E2F1开始转录下游细胞周期相关基因推动细胞周期进程。cyclinE1通过与CDK2结合使细胞周期进入S期进行DNA合成。小分子量cyclinE1的高表达[63]和Rb蛋白低表达[64]可预测哌柏西利耐药。PALOMA-3子研究证实,cyclinE1的表达与哌柏西利联合氟维司群的耐药以及哌柏西利治疗后的抗增殖作用降低有关[65]。人源性肿瘤组织异种移植模型(patient-derived tumor xenograft,PDX)进一步证实了*CCNE*1(编码cyclinE1的基因)扩增或*RB*1缺失可引起CDK4/6抑制剂获得性耐药[66]。其相关治疗靶点的研究还有待后续报道。

3 结论

CDK4/6抑制剂从细胞周期、衰老和免疫等途径多维度发挥抗肿瘤作用,其对细胞周期以外途径的影响也是未来探索其敏感性和耐药机制过程中需要继续挖掘的方向。对于CDK4/6抑制剂进展后的治疗策略,CDK4/6抑制剂跨线治疗、新型口服SERDs、CDK4/6抑制剂耐药通路相关的靶向药物、免疫治疗、HDAC抑制剂等方案都值得后续前瞻性、大样本临床研究的进一步探索,未来或可通过监测患者相应的生物标志物的动态变化个性化地制定治疗策略。

参考文献(References)

[1] Finn R S, Aleshin A, Slamon D J. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers[J]. Breast Cancer Research, 2016, 18(1): 17.

[2] Sherr C J. Cancer cell cycles[J]. Science, 1996, 274(5293): 1672-1677.

[3] Lange C A, Yee D. Killing the second messenger: Targeting loss of cell cycle control in endocrine-resistant breast cancer[J]. Endocrine-Related Cancer, 2011, 18(4): C19-C24.

[4] Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: A changing paradigm[J]. Nature Review Cancer, 2009, 9 (3): 153-166.

[5] Rubin S M, Sage J, Skotheim J M. Integrating old and new paradigms of G1/S control[J]. Molecular Cell, 2020, 80(2): 183-192.

[6] Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)[J]. Annals of Oncology, 2020, 31 (12): 1623-1649.

[7] Gradishar W J, Moran M S, Abraham J, et al. Breast cancer, version 3.2022, NCCN clinical practice guidelines in oncology[J]. Journal of the National Comprehensive Cancer Network, 2022, 20(6): 691-722.

[8] Rugo H S, Finn R S, Dieras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up[J]. Breast Cancer Research and Treatment, 2019, 174(3): 719-729.

[9] Tripathy D, Im S A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): A randomised phase 3 trial[J]. The Lancet Oncology, 2018, 19(7): 904-915.

[10] Goetz M P, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer[J]. Journal of Clinical Oncology, 2017, 35(32): 3638-3646.

[11] Finn R S, Martin M, Rugo H S, et al. Palbociclib and letrozole in advanced breast cancer[J]. The New England Journal of Medicine, 2016, 375(20): 1925-1936.

[12] Xu B, Hu X, Li W, et al. Palbociclib plus letrozole versus placebo plus letrozole in Asian postmenopausal women with oestrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: primary results from PALOMA-4[J]. European Journal of Cancer, 2022, 175: 236-245.

[13] Fabi A, Ciccarese M, Scagnoli S, et al. Post-progression treatments after palbociclib plus endocrine therapy in HR+/HER2- metastatic breast cancer patients: What is the better choice?[J]. Oncology, 2021.

[14] Wander S A, Han H S, Zangardi M L, et al. Clinical outcomes with abemaciclib after prior CDK4/6 inhibitor progression in breast cancer: A multicenter experience[J]. Journal of the National Comprehensive Cancer Network, 2021: 1-8.

[15] Martin J M, Handorf E A, Montero A J, et al. Systemic therapies following progression on first-line CDK4/6-inhibitor treatment: analysis of real-world data[J]. Oncologist, 2022, 27(6): 441-446.

[16] Kalinsky K, Accordino M K, Chiuzan C, et al. Randomized phase II trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: MAINTAIN trial[J]. Journal of Clinical Oncology, 2023, 41(24): 4004-4013.

[17] Fribbens C, O'Leary B, Kilburn L, et al. Plasma *ESR*1 mutations and the treatment of estrogen receptor-positive advanced breast cancer[J]. Journal of Clinical Oncology, 2016, 34(25): 2961-2968.

[18] Lu Y, Liu W. Selective estrogen receptor degraders (SERDs): A promising strategy for estrogen receptor positive endocrine-resistant breast cancer[J]. Journal of Medical Chemistry, 2020, 63(24): 15094-15114.

[19] Bidard F C, Hardy-Bessard A C, Dalenc F, et al. Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising *ESR*1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial[J]. The Lancet Oncology, 2022, 23(11): 1367-1377.

[20] Bidard F C, Kaklamani V G, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial[J]. Journal of Clinical Oncology, 2022, 40(28): 3246-3256.

[21] Liang J, Zbieg J R, Blake R A, et al. GDC-9545 (giredestrant): A potent and orally bioavailable selective estrogen receptor antagonist and degrader with an exceptional preclinical profile for ER+ breast cancer[J]. Journal of Medical Chemistry, 2021, 64(16): 11841-11856.

[22] Jimenez MM, Lim E, Gregor MC, et al. Giredestrant (GDC-9545) vs physician choice of endocrine monotherapy (PCET) in patients (pts) with ER+, HER2-locally advanced/metastatic breast cancer (LA/mBC): Primary analysis of the phase 2, randomised, open-label

acelERA BC study[J]. Annals of Oncology, 2022, 33 (S7): S633-S634.

[23] Tolaney S M, Chan A, Petrakova K, et al. AMEERA-3: Randomized phase II study of amcenestrant (oral selective estrogen receptor degrader) versus standard endocrine monotherapy in estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer[J]. Journal of Clinical Oncology, 2023, 41 (24): 4014-4024.

[24] Ciruelos Gil E M. Targeting the PI3K/AKT/mTOR pathway in estrogen receptor-positive breast cancer[J]. Cancer Treatment Reviews, 2014, 40(7): 862-871.

[25] Mosele F, Stefanovska B, Lusque A, et al. Outcome and molecular landscape of patients with PIK3CA-mutated metastatic breast cancer[J]. Annals of Oncology, 2020, 31(3): 377-386.

[26] Abu-Khalaf M M, Alex Hodge K, Hatzis C, et al. AKT/mTOR signaling modulates resistance to endocrine therapy and CDK4/6 inhibition in metastatic breast cancers [J]. NPJ Precision Oncology, 2023, 7(1): 18.

[27] Michaloglou C, Crafter C, Siersbaek R, et al. Combined inhibition of mTOR and CDK4/6 is required for optimal blockade of E2F function and long-term growth inhibition in estrogen receptor-positive breast cancer[J]. Molecular Cancer Therapy, 2018, 17(5): 908-920.

[28] Cai Z, Wang J, Li Y, et al. Overexpressed cyclin D1 and CDK4 proteins are responsible for the resistance to CDK4/6 inhibitor in breast cancer that can be reversed by PI3K/mTOR inhibitors[J]. Science China-Life Sciences, 2023, 66(1): 94-109.

[29] O′Brien N A, McDermott M S J, Conklin D, et al. Targeting activated PI3K/mTOR signaling overcomes acquired resistance to CDK4/6-based therapies in preclinical models of hormone receptor-positive breast cancer [J]. Breast Cancer Research, 2020, 22(1): 89.

[30] Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer[J]. The New England Journal of Medicine [J]. 2019, 380(20): 1929-1940.

[31] Rugo H S, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): One cohort of a phase 2, multicentre, open-label, non-comparative study[J]. Lancet Oncology, 2021, 22(4): 489-498.

[32] Turner N C, Oliveira M, Howell S J, et al. Capivasertib in hormone receptor-positive advanced breast cancer[J]. The New England Journal of Medicine, 2023, 388(22): 2058-2070.

[33] Bardia A, Hurvitz S A, DeMichele A, et al. Phase I/II trial of exemestane, ribociclib, and everolimus in women with HR(+)/HER2(-) advanced breast cancer after progression on CDK4/6 inhibitors (TRINITI-1)[J]. Clinical Cancer Research, 2021, 27(15): 4177-4185.

[34] Chen Z, Wang Y, Warden C, et al. Cross-talk between ER and HER2 regulates c-MYC-mediated glutamine metabolism in aromatase inhibitor resistant breast cancer cells[J]. Journal of Steroid Biochemistry and Molecular Biology, 2015, 149: 118-127.

[35] Giuliano M, Trivedi M V, Schiff R. Bidirectional crosstalk between the estrogen receptor and human epidermal growth factor receptor 2 signaling pathways in breast cancer: molecular basis and clinical implications[J]. Breast Care (Basel), 2013, 8(4): 256-262.

[36] Vigano L, Locatelli A, Ulisse A, et al. Modulation of the estrogen/erbB2 receptors cross-talk by CDK4/6 inhibition triggers sustained senescence in estrogen receptor- and ErbB2-positive breast cancer[J]. Clinical Cancer Research, 2022, 28(10): 2167-2179.

[37] Wander S A, Cohen O, Gong X, et al. The genomic landscape of intrinsic and acquired resistance to cyclin-dependent kinase 4/6 inhibitors in patients with hormone receptor-positive metastatic breast cancer[J]. Cancer Discovery, 2020, 10(8): 1174-1193.

[38] Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer[J]. The New England Journal of Medicine, 2022, 387(1): 9-20.

[39] Goldenberg D M, Stein R, Sharkey R M. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target[J]. Oncotarget, 2018, 9(48): 28989-29006.

[40] Aslan M, Hsu E C, Garcia-Marques F J, et al. Oncogene-mediated metabolic gene signature predicts breast cancer outcome[J]. NPJ Breast Cancer, 2021, 7(1): 141.

[41] Kalinsky K, Diamond J R, Vahdat L T, et al. Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: Final results from a phase I/II, single-arm, basket trial[J]. Annals of Oncology, 2020, 31(12): 1709-1718.

[42] Rugo H S, Schmid P, Tolaney S M, et al. Health-related quality of life (HRQoL) in the phase III TROPiCS-02

trial of sacituzumab govitecan (SG) vs chemotherapy in HR+ /HER2−metastatic breast cancer (MBC)[J]. Annals of Oncology, 2022, 33(S7): S713−S742.

[43] Willems E, Dedobbeleer M, Digregorio M, et al. The functional diversity of Aurora kinases: A comprehensive review[J]. Cell Division, 2018, 13: 7.

[44] D′Assoro A B, Liu T, Quatraro C, et al. The mitotic kinase Aurora−a promotes distant metastases by inducing epithelial−to−mesenchymal transition in ERalpha(+) breast cancer cells[J]. Oncogene, 2014, 33(5): 599−610.

[45] Haddad T C, Suman V J, D′Assoro A B, et al. Evaluation of alisertib alone or combined with fulvestrant in patients with endocrine−resistant advanced breast cancer: The phase 2 TBCRC041 randomized clinical trial[J]. JAMA Oncology, 2023, 9(6): 815−824.

[46] Falkenberg K J, Johnstone R W. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders[J]. Nature Reviews Drug Discovery, 2014, 13(9): 673−691.

[47] Jiang Z, Li W, Hu X, et al. Tucidinostat plus exemestane for postmenopausal patients with advanced, hormone receptor−positive breast cancer (ACE): A randomised, double−blind, placebo−controlled, phase 3 trial [J]. Lancet Oncology, 2019, 20(6): 806−815.

[48] Li Y, Li W, Gong C, et al. A multicenter analysis of treatment patterns and clinical outcomes of subsequent therapies after progression on palbociclib in HR+/ HER2− metastatic breast cancer[J]. Therapeutic Advances in Medical Oncology, 2021, 13: 17588359211022890.

[49] Zhou J, Wu X, Zhang H, et al. Clinical outcomes of tucidinostat−based therapy after prior CDK4/6 inhibitor progression in hormone receptor−positive heavily pretreated metastatic breast cancer[J]. Breast, 2022, 66: 255−261.

[50] Zhang J, Bu X, Wang H, et al. Cyclin D−CDK4 kinase destabilizes PD−L1 via cullin 3−SPOP to control cancer immune surveillance[J]. Nature, 2018, 553(7686): 91−95.

[51] Tarrado−Castellarnau M, de Atauri P, Tarrago−Celada J, et al. De novo MYC addiction as an adaptive response of cancer cells to CDK4/6 inhibition[J]. Molecular Systems Biology, 2017, 13(10): 940.

[52] Casey S C, Baylot V, Felsher D W. The MYC oncogene is a global regulator of the immune response[J]. Blood, 2018, 131(18): 2007−2015.

[53] Casey S C, Tong L, Li Y, et al. MYC regulates the antitumor immune response through CD47 and PD−L1[J]. Science, 2016, 352(6282): 227−231.

[54] Schaer D A, Beckmann R P, Dempsey J A, et al. The CDK4/6 inhibitor abemaciclib induces a T cell inflamed tumor microenvironment and enhances the efficacy of PD−L1 checkpoint blockade[J]. Cell Reports, 2018, 22 (11): 2978−2994.

[55] Burkhart D L, Sage J. Cellular mechanisms of tumour suppression by the retinoblastoma gene[J]. Nature Reviews Cancer, 2008, 8(9): 671−682.

[56] Smirnov A, Panatta E, Lena A, et al. FOXM1 regulates proliferation, senescence and oxidative stress in keratinocytes and cancer cells[J]. Aging (Albany NY), 2016, 8 (7): 1384−1397.

[57] Deng J, Wang E S, Jenkins R W, et al. CDK4/6 inhibition augments antitumor immunity by enhancing T−cell activation[J]. Cancer Discovery, 2018, 8(2): 216−233.

[58] Lelliott E J, Kong I Y, Zethoven M, et al. CDK4/6 inhibition promotes antitumor immunity through the induction of T−cell memory[J]. Cancer Discovery, 2021, 11 (10): 2582−2601.

[59] Wagner V, Gil J. Senescence as a therapeutically relevant response to CDK4/6 inhibitors[J]. Oncogene, 2020, 39(29): 5165−5176.

[60] Hu Q, Peng J, Jiang L, et al. Metformin as a senostatic drug enhances the anticancer efficacy of CDK4/6 inhibitor in head and neck squamous cell carcinoma[J]. Cell Death & Disease, 2020, 11(10): 925.

[61] Formisano L, Lu Y, Servetto A, et al. Aberrant FGFR signaling mediates resistance to CDK4/6 inhibitors in ER+ breast cancer[J]. Nature Communications, 2019, 10 (1): 1373.

[62] Mao P, Cohen O, Kowalski K J, et al. Acquired FGFR and FGF alterations confer resistance to estrogen receptor (ER) targeted therapy in ER(+) metastatic breast cancer[J]. Clinical Cancer Research, 2020, 26(22): 5974−5989.

[63] Karakas C, Biernacka A, Bui T, et al. Cytoplasmic cyclin E and phospho−cyclin−dependent kinase 2 are biomarkers of aggressive breast cancer[J]. American Journal of Pathology, 2016, 186(7): 1900−1912.

[64] Chou A, Froio D, Nagrial A M, et al. Tailored first−line and second−line CDK4−targeting treatment combinations in mouse models of pancreatic cancer[J]. Gut, 2018, 67(12): 2142−2155.

[65] Turner N C, Liu Y, Zhu Z, et al. Cyclin E1 expression and palbociclib efficacy in previously treated hormone

receptor-positive metastatic breast cancer[J]. Journal of Clinical Oncology, 2019, 37(14): 1169-1178.
[66] Herrera-Abreu M T, Palafox M, Asghar U, et al. Early adaptation and acquired resistance to CDK4/6 inhibition in estrogen receptor-positive breast cancer[J]. Cancer Research, 2016, 76(8): 2301-2313.

Advances of subsequent therapeutic strategies to overcome resistance to CDK4/6 inhibitors in breast cancer and its mechanisms

MA Jiayi, YIN Wenjin, WU Ziping, LU Jingsong*

Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

Abstract This article provided an overview of current therapeutic strategies to overcome CDK4/6 inhibitor resistance in breast cancer and analyzed the clinical findings of CDK4/6 inhibitor cross-line therapy, novel oral SERDs, PI3K/AKT/mTOR inhibitors, ADC drugs, AURKA inhibitors, HDAC inhibitors, immunotherapeutic strategies and anti-senescence therapies after CDK4/6 inhibitor progression and the related mechanisms. Furthermore, we prospected the potential targets for clinical studies in the future.

Keywords cyclin-dependent kinase 4/6 inhibitor; advanced breast cancer; mechanisms of drug resistance; endocrine therapy

（责任编辑　王丽娜）