DOI: 10.12280/gjfckx.20220089

·综　述·

*CCNE*1基因在卵巢高级别浆液性癌中的研究进展

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【摘　要】 细胞周期蛋白E1（Cyclin E1，*CCNE*1）基因扩增是卵巢高级别浆液性癌（high-grade serous ovarian carcinoma，HGSOC）最常见的拷贝数变异之一，扩增率为20%左右。*CCNE*1基因扩增不仅参与HGSOC的早期癌前病变，促进恶性肿瘤的发生、发展，还可引起细胞周期紊乱和染色体不稳定，从而增加HGSOC的铂类耐药性和复发率，最终导致患者的化疗效果不佳和预后较差。为改善*CCNE*1扩增的HGSOC患者的预后和生活质量，在暂时没有*CCNE*1扩增的HGSOC的靶向治疗药物的情况下，使用细胞周期蛋白依赖性激酶2（cyclin-dependent kinases 2，CDK2）小分子抑制剂或者多腺苷二磷酸核糖聚合酶[poly (ADP-ribose) polymerase，PARP]抑制剂与其他药物联合治疗，一定程度上能有效地抑制肿瘤细胞的增殖活性，促进肿瘤细胞死亡。因此，从*CCNE*1扩增对HGSOC的早期发病机制的影响和产生铂类耐药的角度上来说，*CCNE*1基因有望成为HGSOC的潜在治疗靶标和预后评价生物学指标，在改善患者的治疗和预后方面具有重要意义。

【关键词】 卵巢肿瘤；细胞周期蛋白E；基因扩增；药物疗法；预后；卵巢高级别浆液性癌

Research Progress of *CCNE*1 Gene in High-Grade Serous Ovarian Carcinoma

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【Abstract】 CyclinE1 (*CCNE*1) gene amplification is one of the most common copy number variations in high-grade serous ovarian carcinoma (HGSOC), with an amplification rate of about 20%. *CCNE*1 gene amplification not only participates in the early precancerous lesions of HGSOC and promotes the occurrence and development of malignant tumors, but also causes cell cycle disorder and chromosome instability, thus increasing platinum resistance and recurrence rate of HGSOC, and ultimately leading to poor chemotherapy effect and poor prognosis of patients. In order to improve the prognosis and quality of life of patients with *CCNE*1-amplified HGSOC, cyclin-dependent kinases 2 (CDK2) small molecule inhibitors or poly (ADP-ribose) polymerase (PARP) inhibitors in combination with other drugs are used to treat *CCNE*1-amplified HGSOC in the absence of targeted drugs for *CCNE*1-amplified HGSOC. To a certain extent, it can effectively inhibit the proliferation of tumor cells and promote the death of tumor cells. Therefore, *CCNE*1 gene is expected to become a potential therapeutic target and prognostic biological indicator of HGSOC from the perspective of the influence of *CCNE*1 amplification on the

基金项目：山西省自然科学基金（201901D111210）

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[21] Lee M, Kim SW, Paek J, et al. Comparisons of surgical outcomes, complications, and costs between laparotomy and laparoscopy in early-stage ovarian cancer[J]. Int J Gynecol Cancer, 2011, 21(2): 251-256. doi: 10.1097/IGC.0b013e318208c71c.

[22] Dioun S, Wu J, Chen L, et al. Intraoperative Rupture of the Ovarian Capsule in Early-Stage Ovarian Cancer: A Meta-analysis [J]. Obstet Gynecol, 2021, 138(2): 261-271. doi: 10.1097/AOG.0000000000004455.

[23] Ndofor BT, Soliman PT, Schmeler KM, et al. Rate of port-site metastasis is uncommon in patients undergoing robotic surgery for gynecological malignancies[J]. Int J Gynecol Cancer, 2011, 21(5): 936-940. doi: 10.1097/IGC.0b013e3182174609.

[24] Kong Q, Wei H, Zhang J, et al. Comparison of the survival outcomes of laparoscopy versus laparotomy in treatment of early-stage ovarian cancer: a systematic review and meta-analysis[J]. J Ovarian Res, 2021, 14(1): 45. doi: 10.1186/s13048-021-00793-1.

（收稿日期：2021-07-26）

[本文编辑　杨晓园]

early pathogenesis of HGSOC and the generation of platinum resistance, which is of great significance to improve the treatment and prognosis of patients.

【**Keywords**】 Ovarian neoplasms; Cyclin E; Gene amplification; Drug therapy; Prognosis; High-grade serous ovarian carcinoma

(*J Int Obstet Gynecol*, 2022, 49:286-290)

卵巢高级别浆液性癌(high-grade serous ovarian carcinoma,HGSOC) 是上皮性卵巢癌(epithelial ovarian cancer,EOC)最常见的组织学亚型之一,约占所有 EOC 的 75%,具有基因组不稳定性、高度侵袭性和预后较差等特征[1]。目前,HGSOC 的标准治疗方式是手术切除后接受铂类联合紫杉烷类药物化疗,但 80%的患者易出现复发,约 40%~60%的患者对化疗敏感,25%的患者会对铂类产生耐药性[2]。可见,这些化疗药物对部分 HGSOC 患者具有一定的敏感性,但大多数 HGSOC 患者经化疗后易出现复发,这在一定程度上影响了 HGSOC 患者的生活质量。因此,为了提高 HGSOC 的诊断水平和改善 HGSOC 患者的生活质量,亟需探索和开发具有临床应用价值的治疗靶标。

细胞周期蛋白 E1(Cyclin E1,*CCNE*1)基因扩增是 HGSOC 最常见的基因拷贝数变异之一,约 20%的 HGSOC患者存在*CCNE*1扩增[3]。*CCNE*1基因常在卵巢癌[4]、子宫内膜癌[5]、骨肉瘤[6]和乳腺癌[7]等恶性肿瘤中发生扩增,扩增率为2%~40%。同时,*CCNE*1基因扩增不仅是这些恶性肿瘤的致癌和预后不良的因素,还与HGSOC耐药密切相关。因此,现就*CCNE*1基因与HGSOC发生、发展、耐药和预后不良的关系以及HGSOC的靶向治疗药物等方面进行综述。

1　*CCNE*1扩增与HGSOC发生、发展的关系

HGSOC是一种高度异质性和基因组不稳定的疾病,约20%的HGSOC出现*CCNE*1扩增,*CCNE*1扩增对HGSOC的发生、发展具有重要意义[3,8]。近年研究表明HGSOC大多起源于输卵管上皮分泌型细胞,而不是卵巢表面上皮[9-10]。输卵管上皮分泌型细胞对DNA损伤较为敏感,当DNA受到各种毒性因素刺激时,分泌型上皮细胞无法及时修复DNA,会造成大量DNA损伤蓄积,使细胞发生*TP*53基因突变,促进输卵管上皮分泌型细胞异型增生,逐渐形成浆液性输卵管上皮内癌(serous tubal intraepithelial carcinoma,STIC),随后癌细胞直接种植到卵巢表面后进展成HGSOC。*TP*53突变是发生癌变的一个初始事件,参与肿瘤的发生、发展,但只是*TP*53突变不足以使细胞恶变,还需要其他分子生物学的改变来共同促使早期STIC发展至HGSOC。*CCNE*1基因和*TP*53基因之间在体内外实验中都存在协同致癌作用,*CCNE*1基因去调控后会使TP53蛋白缺陷的输卵管分泌型上皮细胞获得恶性表型,从而促进肿瘤不受控制地生长[11]。然而,*CCNE*1扩增一般发生在*TP*53突变的早期,这种早期扩增可能提示HGSOC的癌前病变存在DNA拷贝数异常改变[12]。Kuhn等[13]比较STIC和HGSOC的*CCNE*1扩增率发现两者无显著差异,这表明发生癌前病变时已出现*CCNE*1扩增。由此可见,*CCNE*1扩增对癌前病变发生恶性转化至关重要,是HGSOC发生、发展的重要分子事件,可作为早期筛查的潜在靶点。

2　*CCNE*1扩增与HGSOC耐药的关系

2.1　细胞周期　细胞周期是指细胞从一次分裂完成后开始至下一次分裂结束的全过程。正常细胞周期是由细胞周期蛋白和CDKs构成,共同完成细胞分裂与增殖[14]。*CCNE*1基因编码的Cyclin E1是视网膜母细胞瘤(retinoblastoma,RB)蛋白抑制通路的关键调节因子,主要参与细胞周期的调控。Cyclin E1主要通过打开三磷酸腺苷结合域,促使三磷酸腺苷和底物进入CDKs活性位点,与CDKs家族成员中亲和力最高的CDK2结合后形成Cyclin E1/CDK2复合体,并磷酸化下游RB靶点使RB蛋白失活,从而释放出早期转录因子2(early 2 transcription factor,E2F),使细胞从G1期过渡到S期,促进细胞进行正常的DNA复制和细胞增殖[11]。细胞周期紊乱是人类发生恶性肿瘤和产生铂类耐药的原因之一。一般而言,细胞周期蛋白表达量的改变会引起肿瘤细胞异常增殖和分裂,从而导致基因组不稳定和化疗耐药性[15-16]。当*CCNE*1发生扩增时会促进Cyclin E1表达量增多,加快细胞分裂与增殖的同时可引发DNA不受控制地进行复制,从而破坏胞质分裂稳态,导致肿瘤细胞发生异常增殖和耐药性[17-19];*CCNE*1扩增的肿瘤不但本身可以增加化疗耐药性,还可以赋予具有高增殖和低凋亡活性的肿瘤细胞一定的生长优势,增强肿瘤细胞的增殖能力,加快有丝分裂,促进肿瘤细胞的生长[20]。如上所述,肿瘤细胞异常增殖与HGSOC铂类耐药性密切相关,也是间接造成HGSOC患者复发和预后不良的原因之一。

2.2　染色体不稳定（chromosome instability）　染色体不稳定是指增加或丢失整个或大部分染色体的速率，是基因组不稳定的主要形式之一。在一定程度上，*CCNE*1基因拷贝数变异意味着会发生染色体不稳定性，其中Cyclin E1/CDK2复合体与染色体不稳定密切相关。Cyclin E1/CDK2复合体主要通过2种方式来调控染色体不稳定：①参与中心体扩增。Cyclin E1/CDK2复合体的激活与中心体复制有关，主要通过磷酸化核磷酸蛋白（nucleophosmin，NPM），促使NPM从中心体内释放，启动中心体复制；但当NPM无法进行去磷酸化时，会形成2个以上的中心体，即中心体扩增，这不仅对胞质分裂造成严重干扰，还会导致染色体发生分离错误[21]。②参与有丝分裂G1/S期检查点的损伤。正常情况下，Cyclin E1受转录水平和蛋白酶体活性的严格调控。当Cyclin E1/CDK2复合体变得活跃时，Cyclin E1主要依赖G1后期完成E2F转录和S期泛素介导的蛋白水解。然而，Cyclin E1过表达会引起G1/S期检查点失控，无法激活有丝分裂蛋白水解酶，使细胞延迟进入有丝分裂后期，这可能会导致染色体错配和非整倍性[22]。值得注意的是，染色体不稳定不仅与肿瘤的恶变和异质性有关，还与HGSOC的复发、耐药和预后不良有关。Penner-Goeke等[23]研究发现在PEO4和A2780cp这2种EOC的耐药模型中均出现染色体不稳定，并与EOC的耐药性和复发性有关。最新一项研究也证实了染色体不稳定的存在与促进肿瘤的发生、发展、转移和耐药性有关[24]。

3　*CCNE*1扩增与HGSOC预后不良的关系

鉴于HGSOC常出现铂类耐药和复发等情况，有学者提出*CCNE*1扩增联合Cyclin E1高表达可作为HGSOC预后不良的预测生物标志物[25-26]。Filippova等[27]研究表明患有HGSOC的年轻女性易发生乳腺癌易感基因1/2（breast cancer 1 and 2，*BRCA* 1/2）突变，而*CCNE*1扩增常见于HGSOC的中老年女性，并可能与其预后不良有关。*CCNE*1扩增和同源重组修复基因*BRCA* 1/2突变在HGSOC中是相互排斥的，*BRCA* 1/2突变的HGSOC对铂类药物较敏感，但发生*CCNE*1扩增的HGSOC对铂类药物易耐药，对多腺苷二磷酸核糖聚合酶[poly (ADP-ribose) polymerase，PARP]抑制剂的反应有限，因此，患有HGSOC的中老年患者接受铂类及PARP抑制剂治疗效果较差。另有研究利用干扰RNA敲低*CCNE*1基因表达水平后，发现*CCNE*1基因下调会导致原先Cyclin E1蛋白过表达的OVCAR3和OVCAR5等4种卵巢癌细胞系出现细胞生长率下降65%~90%[28]。此外，*CCNE*1扩增不仅促进HGSOC细胞的生长，还能评估患者的疗效和预后情况。Nakayama等[29]对接受铂类和紫杉烷类化疗的卵巢癌患者进行研究发现，*CCNE*1扩增与总生存期缩短、预后不良有关，但Cyclin E1高表达与总体存活率无关。由此可见，Cyclin E1高表达不能作为HGSOC患者新辅助治疗或铂类联合紫杉烷类化疗产生耐药性的预测标志物，并且*CCNE*1无扩增合并Cyclin E1高表达的HGSOC患者较*CCNE*1扩增合并Cyclin E1高表达的患者预后较好[3, 30]。这是因为*CCNE*1无扩增合并Cyclin E1高表达的HGSOC患者可能存在同源重组缺陷（homologous recombination deficiency，HRD），所以使用铂类化疗药物治疗较为敏感。总之。HGSOC患者不能以Cyclin E1高表达作为预后指标，但以*CCNE*1基因为治疗靶点可能有利于改善预后和提高总体生存率。

4　*CCNE*1扩增与HGSOC的靶向治疗药物

4.1　CDK2小分子抑制剂　CDK2小分子抑制剂主要通过阻碍CDK2与Cyclin E1形成Cyclin E1/CDK2复合体来抑制细胞异常增殖，从而改善HGSOC患者的不良预后和降低其铂类耐药性。*CCNE*1扩增的HGSOC细胞系对干扰RNA敲低的CDK2具有选择性敏感，提示CDK2可能是*CCNE*1扩增的HGSOC的潜在治疗药物[31]。Yang等[28]发现CCNE1蛋白过表达的卵巢癌细胞对CDK2抑制剂SNS-032的敏感性是没有Cyclin E1蛋白过表达的卵巢癌细胞的40倍，SNS-032可通过抑制Cyclin E1蛋白过表达的卵巢癌细胞的转移，从而延长Cyclin E1蛋白过表达的卵巢癌小鼠的总体生存期。因此，该研究表明CDK2抑制剂可以有效地抑制Cyclin E1蛋白过表达的卵巢癌细胞的生长。然而，*CCNE*1扩增的卵巢癌也会对CDK2抑制剂产生耐药性，使其对CDK2抑制剂的敏感性显著降低，这可能存在2种旁路耐药机制：一是CDK2蛋白的上调，二是与选择多倍体细胞有关[32]。目前，考虑到单用CDK2抑制剂治疗*CCNE*1扩增的卵巢癌的敏感性下降，有学者提出联合其他协同药物来减少耐药性和不良反应。Au-Yeung等[31]通过美国的癌症基因组图谱（The Cancer Genome Atlas，TCGA）证实了*CCNE*1和蛋白激酶B2（protein kinase B2，*AKT*2）在HGSOC中存在共扩增，随后利用高通量药物筛选出CDK2抑制剂（Dinaciclib）和AKT抑制剂（MK-2206）具有药物协同增效作用，该研究表明Dinaciclib和MK-2206的新型组合可以选择性靶向治疗*CCNE*1扩增的HGSOC。由此可见，CDK2抑制剂联合其他协同药物为治疗

*CCNE*1扩增的HGSOC提供了一种崭新思路。

4.2　PARP抑制剂　近年来，已批准的PARP抑制剂药物分别有奥拉帕尼（Olaparib）、尼拉帕尼（Niraparib）和鲁卡帕尼（Rucaparib）。该类药物主要用于铂类化疗后复发性与铂类耐药性的EOC患者的维持治疗[33-34]。一项Meta分析结果表明，PARP抑制剂已被用作晚期HGSOC患者一线治疗后的维持治疗，PARP抑制剂维持治疗可使HGSOC患者的死亡风险降低46%[35]。然而，PARP抑制剂主要是针对治疗*BRCA* 1/2突变的HGSOC具有高度敏感性，但对*CCNE*1扩增的HGSOC进行长期治疗的效果欠佳，甚至可能会产生耐药。有研究表明抗血管生成单克隆抗体（Bevacizumab）联合PARP抑制剂可降低耐药性，并推荐作为晚期卵巢癌的一线治疗药物[36]。因此，有学者提出PARP抑制剂与抗血管生成药物或其他协同药物联合应用可以有效地提高疗效。Kim等[37]研究表明PARP抑制剂联合共济失调毛细血管扩张症突变和 Rad3相关（ataxia telangiectasia mutated and Rad3-related，ATR）抑制剂（ATRi）能显著地抑制肿瘤快速生长和延长总体生存期。ATRi 联合 PARP抑制剂在新发性或获得性的铂类耐药且发生*CCNE*1扩增的卵巢癌模型中具有药物协同作用，ATRi（AZD6738）不仅能使HGSOC的肿瘤细胞重新对Olaparib敏感，还能使DNA复制叉停滞和细胞凋亡。最近，Gupta等[38]研究发现Olaparib联合选择性HDAC1/2抑制剂（Entinostat）治疗*CCNE*1扩增的HGSOC小鼠的耐受性良好，并能明显提高小鼠的存活率。Entinostat不仅能通过延缓DNA复制叉的进展来导致不可逆转的DNA损伤和细胞死亡，还能增强Olaparib药效来大幅度降低卵巢癌的细胞活性。目前PARP抑制剂治疗卵巢癌患者取得了显著的疗效，同时PARP抑制剂联合其他协同药物也为治疗*CCNE*1扩增的HGSOC提供了一种科学合理的策略。

5　结语与展望

*CCNE*1扩增与HGSOC的发生、发展、化疗耐药和预后不良密切相关，被认为是HGSOC化疗耐药的预测标志物和潜在的治疗靶标。CDK2小分子抑制剂或PARP抑制剂联合其他药物在治疗HGSOC方面已取得了一定的成效，但长期使用此类药物治疗*CCNE*1扩增的HGSOC可能会产生耐药性，严重影响患者预后。然而，*CCNE*1扩增的HGSOC产生耐药的作用机制尚未十分明确，暂时没有以*CCNE*1为靶向治疗的特效药物，因此有必要对发生*CCNE*1扩增的HGSOC的耐药机制进行深入探讨。随着研究的不断深入，未来以*CCNE*1为治疗靶标可能有助于改善HGSOC患者的预后和提高患者的生活质量。

参　考　文　献

[1] Kroeger PT Jr, Drapkin R. Pathogenesis and heterogeneity of ovarian cancer[J]. Curr Opin Obstet Gynecol, 2017, 29(1): 26-34. doi: 10.1097/GCO.0000000000000340.

[2] Gorski JW, Ueland FR, Kolesar JM. CCNE1 Amplification as a Predictive Biomarker of Chemotherapy Resistance in Epithelial Ovarian Cancer[J]. Diagnostics (Basel), 2020, 10(5): 279. doi: 10.3390/diagnostics10050279.

[3] Sapoznik S, Aviel-Ronen S, Bahar-Shany K, et al. CCNE1 expression in high grade serous carcinoma does not correlate with chemoresistance[J]. Oncotarget, 2017, 8(37): 62240-62247. doi: 10.18632/oncotarget.19272.

[4] Patch AM, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer [J]. Nature, 2015, 521(7553): 489-494. doi: 10.1038/nature14410.

[5] Li Y, Li L. Bioinformatic screening for candidate biomarkers and their prognostic values in endometrial cancer [J]. BMC Genet, 2020, 21(1): 113. doi: 10.1186/s12863-020-00898-4.

[6] Schott C, Shah AT, Sweet-Cordero EA. Genomic Complexity of Osteosarcoma and Its Implication for Preclinical and Clinical Targeted Therapies [J]. Adv Exp Med Biol, 2020, 1258: 1-19. doi: 10.1007/978-3-030-43085-6_1.

[7] Zhao ZM, Yost SE, Hutchinson KE, et al. CCNE1 amplification is associated with poor prognosis in patients with triple negative breast cancer[J]. BMC Cancer, 2019, 19(1): 96. doi: 10.1186/s12885-019-5290-4.

[8] Integrated genomic analyses of ovarian carcinoma [J]. Nature, 2011, 474(7353): 609-615. doi: 10.1038/nature10166.

[9] Li J, Fadare O, Xiang L, et al. Ovarian serous carcinoma: recent concepts on its origin and carcinogenesis [J]. J Hematol Oncol, 2012, 5: 8. doi: 10.1186/1756-8722-5-8.

[10] Piek JM, van Diest PJ, Zweemer RP, et al. Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer[J]. J Pathol, 2001, 195(4): 451-456. doi: 10.1002/path.1000.

[11] Karst AM, Jones PM, Vena N, et al. Cyclin E1 deregulation occurs early in secretory cell transformation to promote formation of fallopian tube-derived high-grade serous ovarian cancers [J]. Cancer Res, 2014, 74(4): 1141-1152. doi: 10.1158/0008-5472.CAN-13-2247.

[12] Mei J, Tian H, Huang HS, et al. Cellular models of development of ovarian high-grade serous carcinoma: A review of cell of origin and mechanisms of carcinogenesis [J]. Cell Prolif, 2021, 54(5): e13029. doi: 10.1111/cpr.13029.

[13] Kuhn E, Wang TL, Doberstein K, et al. CCNE1 amplification and centrosome number abnormality in serous tubal intraepithelial carcinoma: further evidence supporting its role as a precursor of ovarian high-grade serous carcinoma[J]. Mod Pathol, 2016, 29(10): 1254-1261. doi: 10.1038/modpathol.2016.101.

[14] Venuto S, Merla G. E3 Ubiquitin Ligase TRIM Proteins, Cell Cycle

and Mitosis[J]. Cells, 2019, 8(5): 510. doi: 10.3390/cells8050510.

[15] Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm[J]. Nat Rev Cancer, 2009, 9(3): 153-166. doi: 10.1038/nrc2602.

[16] Pang W, Li Y, Guo W, et al. Cyclin E: a potential treatment target to reverse cancer chemoresistance by regulating the cell cycle [J]. Am J Transl Res, 2020, 12(9): 5170-5187.

[17] Maloney SM, Hoover CA, Morejon-Lasso LV, et al. Mechanisms of Taxane Resistance[J]. Cancers (Basel), 2020, 12(11): 3323. doi: 10.3390/cancers12113323.

[18] Otsuka I. Mechanisms of High-Grade Serous Carcinogenesis in the Fallopian Tube and Ovary: Current Hypotheses, Etiologic Factors, and Molecular Alterations[J]. Int J Mol Sci, 2021, 22(9): 4409. doi: 10.3390/ijms22094409.

[19] Hanahan D, Weinberg RA. The hallmarks of cancer [J]. Cell, 2000, 100(1): 57-70. doi: 10.1016/s0092-8674(00)81683-9.

[20] Etemadmoghadam D, George J, Cowin PA, et al. Amplicon-dependent CCNE1 expression is critical for clonogenic survival after cisplatin treatment and is correlated with 20q11 gain in ovarian cancer[J]. PLoS One, 2010, 5(11): e15498. doi: 10.1371/journal.pone.0015498.

[21] Hwang HC, Clurman BE. Cyclin E in normal and neoplastic cell cycles[J]. Oncogene, 2005, 24(17): 2776-2786. doi: 10.1038/sj.onc.1208613.

[22] Keck JM, Summers MK, Tedesco D, et al. Cyclin E overexpression impairs progression through mitosis by inhibiting APC (Cdh1)[J]. J Cell Biol, 2007, 178(3): 371-385. doi: 10.1083/jcb.200703202.

[23] Penner-Goeke S, Lichtensztejn Z, Neufeld M, et al. The temporal dynamics of chromosome instability in ovarian cancer cell lines and primary patient samples [J]. PLoS Genet, 2017, 13(4): e1006707. doi: 10.1371/journal.pgen.1006707.

[24] Vishwakarma R, McManus KJ. Chromosome Instability; Implications in Cancer Development, Progression, and Clinical Outcomes [J]. Cancers (Basel), 2020, 12(4): 824. doi: 10.3390/cancers12040824.

[25] Chan AM, Enwere E, McIntyre JB, et al. Combined CCNE1 high-level amplification and overexpression is associated with unfavourable outcome in tubo-ovarian high-grade serous carcinoma [J]. J Pathol Clin Res, 2020, 6(4): 252-262. doi: 10.1002/cjp2.168.

[26] Petersen S, Wilson AJ, Hirst J, et al. CCNE1 and BRD4 co-amplification in high-grade serous ovarian cancer is associated with poor clinical outcomes[J]. Gynecol Oncol, 2020, 157(2): 405-410. doi: 10.1016/j.ygyno.2020.01.038.

[27] Filippova OT, Selenica P, Pareja F, et al. Molecular characterization of high-grade serous ovarian cancers occurring in younger and older women[J]. Gynecol Oncol, 2021, 161(2): 545-552. doi: 10.1016/j.ygyno.2021.02.028.

[28] Yang L, Fang D, Chen H, et al. Cyclin-dependent kinase 2 is an ideal target for ovary tumors with elevated cyclin E1 expression[J]. Oncotarget, 2015, 6(25): 20801-20812. doi: 10.18632/oncotarget.4600.

[29] Nakayama N, Nakayama K, Shamima Y, et al. Gene amplification CCNE1 is related to poor survival and potential therapeutic target in ovarian cancer[J]. Cancer, 2010, 116(11): 2621-2634. doi: 10.1002/cncr.24987.

[30] Aziz D, Etemadmoghadam D, Caldon CE, et al. 19q12 amplified and non-amplified subsets of high grade serous ovarian cancer with overexpression of cyclin E1 differ in their molecular drivers and clinical outcomes[J]. Gynecol Oncol, 2018, 151(2): 327-336. doi: 10.1016/j.ygyno.2018.08.039.

[31] Au-Yeung G, Lang F, Azar WJ, et al. Selective Targeting of Cyclin E1-Amplified High-Grade Serous Ovarian Cancer by Cyclin-Dependent Kinase 2 and AKT Inhibition [J]. Clin Cancer Res, 2017, 23(7): 1862-1874. doi: 10.1158/1078-0432.CCR-16-0620.

[32] Etemadmoghadam D, Au-Yeung G, Wall M, et al. Resistance to CDK2 inhibitors is associated with selection of polyploid cells in CCNE1-amplified ovarian cancer [J]. Clin Cancer Res, 2013, 19(21): 5960-5971. doi: 10.1158/1078-0432.CCR-13-1337.

[33] Mittica G, Ghisoni E, Giannone G, et al. PARP Inhibitors in Ovarian Cancer[J]. Recent Pat Anticancer Drug Discov, 2018, 13(4): 392-410. doi: 10.2174/1574892813666180305165256.

[34] Mirza MR, Coleman RL, González-Martín A, et al. The forefront of ovarian cancer therapy: update on PARP inhibitors [J]. Ann Oncol, 2020, 31(9): 1148-1159. doi: 10.1016/j.annonc.2020.06.004.

[35] Ibrahim EM, Refae AA, Bayer AM, et al. Poly (ADP-ribose) polymerase inhibitors as maintenance treatment in patients with newly diagnosed advanced ovarian cancer: a meta-analysis[J]. Future Oncol, 2020, 16(10): 585-596. doi: 10.2217/fon-2020-0057.

[36] Onstad M, Coleman RL, Westin SN. Movement of Poly-ADP Ribose (PARP) Inhibition into Frontline Treatment of Ovarian Cancer [J]. Drugs, 2020, 80(15): 1525-1535. doi: 10.1007/s40265-020-01382-0.

[37] Kim H, Xu H, George E, et al. Combining PARP with ATR inhibition overcomes PARP inhibitor and platinum resistance in ovarian cancer models[J]. Nat Commun, 2020, 11(1): 3726. doi: 10.1038/s41467-020-17127-2.

[38] Gupta VG, Hirst J, Petersen S, et al. Entinostat, a selective HDAC1/2 inhibitor, potentiates the effects of olaparib in homologous recombination proficient ovarian cancer[J]. Gynecol Oncol, 2021, 162(1): 163-172. doi: 10.1016/j.ygyno.2021.04.015.

（收稿日期：2022-01-30）

[本文编辑　秦娟]