

PARP 抑制剂联合应用抗肿瘤临床前研究进展

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摘要 多腺苷二磷酸核糖聚合酶(PARP)是一类DNA损伤修复酶。PARP抑制剂包括奥拉帕利(AZD2281)、尼拉帕利(MK-4827)、Rucaparib、Veliparib(ABT-888)、Fluzoparib和Talazoparib(BMN-673)等。本文通过检索相关文献,就PARP抑制剂联合应用抗肿瘤的临床前研究进行综述。通过合成致死模式,PARP抑制剂对具有同源重组修复缺陷的肿瘤细胞具有较强的杀伤作用,但对于DNA损伤修复功能完好的肿瘤细胞,PARP抑制剂往往需要与放疗或其他药物联合发挥作用,联合应用的药物包括抗血管生成药物、热休克蛋白90抑制剂、细胞周期蛋白依赖性激酶12抑制剂、免疫检查点抑制剂、组蛋白脱乙酰酶抑制剂等。PARP抑制剂的联合应用有望增强抗肿瘤药物的疗效,实现增敏增效和逆转耐药的目标,值得进一步开展深入研究并探索新的联合治疗方案。

关键词 多腺苷二磷酸核糖聚合酶抑制剂;药物联用;抗肿瘤;临床前研究

Progress in preclinical study of combination of PARP inhibitors against tumor

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ABSTRACT Poly (ADP-ribose) polymerase (PARP) is a kind of DNA damage repair enzyme. PARP inhibitors include Olaparib (AZD2281), Niraparib (MK-4827), Rucaparib, Veliparib (ABT-888), Fluzoparib and Talazoparib (BMN-673), etc. This article reviews the preclinical research on the combined application of PARP inhibitors against tumor by searching the relevant literatures. Through the synthetic lethal mode, PARP inhibitors have a strong killing effect on tumor cells with homologous recombination repair defects. However, for tumor cells with intact DNA damage repair function, PARP inhibitors often need to be combined with radiotherapy or other drugs to play a role. Combined application drugs include antiangiogenic drugs, heat shock protein 90 inhibitors, cyclin-dependent kinase 12 inhibitors, immune checkpoint inhibitors, histone deacetylase inhibitors, etc. The combined application of PARP inhibitors is expected to enhance the efficacy of anti-tumor drugs and achieve the goals of sensitization, synergism and reversal of drug resistance, which is worthy of further in-depth research and exploration of new combined treatment schemes.

KEYWORDS poly (ADP-ribose) polymerase inhibitors; drug combination; anti-tumor; preclinical study

多腺苷二磷酸核糖聚合酶[poly (ADP-ribose) polymerase, PARP]在细胞DNA损伤修复中具有重要作用,即当细胞DNA发生断裂时,PARP可结合到断裂处,募集包括组蛋白在内的烟酰胺腺嘌呤二核苷酸依赖的腺苷二磷酸核糖聚合酶以及其他DNA修复酶,完成受损DNA的修复^[1]。2005年,科学家首次发现了一种可抑制PARP功能的小分子化合物,并将其命名为PARP抑制剂^[2]。有研究表明,该化合物可与突变的乳腺癌易感基因BRCA相互影响,从而导致肿瘤细胞死亡,最终首次实现了PARP抑制剂介导的合成致死^[2]。作为具有革新意义的新型抗肿瘤药,目前已上市的常用PARP抑制剂包括奥拉帕利(AZD2281)、尼拉帕利(MK-4827)、Rucaparib、Veliparib(ABT-888)、Fluzoparib和Talazoparib(BMN-673)等,主要适应证包括乳腺癌、卵巢癌和原发性腹膜癌等,

且上述药物针对前列腺癌、胃癌、肺癌的研究也正在进行中^[3]。

早期关于PARP抑制剂的研究主要集中在单药治疗领域,但有研究指出,PARP抑制剂单独使用具有毒性高、易产生耐药等问题,同时其适应证较为狭窄,临床应用受限^[4];PARP抑制剂对具有同源重组修复缺陷的肿瘤细胞具有较强的杀伤作用,但对DNA损伤修复功能完好的肿瘤细胞杀伤力弱。2010年以来,PARP抑制剂联合应用受到学界越来越多的关注。为了解PARP抑制剂与放疗或其他药物联合应用抗肿瘤的研究进展,笔者综述了PARP抑制剂联合应用的临床前研究现状,以期为该药在恶性肿瘤治疗领域中的应用提供参考。

1 PARP抑制剂联合放疗

放疗是恶性肿瘤的主要治疗手段之一,其作用靶点正是肿瘤细胞的DNA。大量研究表明,PARP抑制剂联合放疗具有良好的协同抗肿瘤效果。Zhan等^[4]研究发现,奥拉帕利联合放疗可诱导人食管腺鳞癌细胞的凋亡并抑制细胞的增殖,且这种抑制效果在乏氧状态下更加

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显著,其相关机制与乏氧状态下细胞同源重组修复(homologous recombination repair, HRR)功能受到抑制以及重组蛋白A(recombination protein A, Rad51)表达下调有关;在裸鼠移植瘤模型实验中,奥拉帕利联合放疗同样具有协同抗肿瘤作用。Park等^[5]在*ARID1A*基因缺失的人子宫内膜癌细胞中发现,奥拉帕利联合低剂量放疗具有体内外协同抗肿瘤作用。在人肺癌和人胰腺癌细胞中,Hastak等^[6]联用PARP抑制剂LT626和放疗后发现,细胞中 γ H2AX和P53蛋白的表达上调,磷酸化毛细血管扩张性共济失调突变蛋白激酶(ataxia-telangiectasia mutated kinase, ATM)、共济失调性毛细血管扩张和RAD3相关蛋白(recombinant ataxia telangiectasia and RAD3 related protein, ATR)的表达增多,提示两者发挥了协同抗肿瘤作用。Wang等^[7]建立了肺癌和乳腺癌小鼠移植瘤模型,发现相较于单纯放疗,尼拉帕利联合放疗可显著抑制肿瘤细胞的生长。

尽管PARP抑制剂联合放疗在恶性肿瘤治疗领域已经取得了一些进展,但目前仍然存在许多问题,主要包括以下几点:(1)PARP抑制剂作为放疗增敏剂的合理剂量范围仍有待确定。已有研究表明,PARP抑制剂结合放疗虽可减少所需的射线剂量,但当前二者的具体结合剂量仍在摸索中^[9]。(2)在临床实际中,是同时进行PARP抑制剂+放疗联合治疗还是经PARP抑制剂治疗后再进行放疗仍有待确定^[4]。(3)迄今为止,用于PARP抑制剂联合放疗疗效判定的生物标志物仍需继续挖掘^[9]。

2 PARP抑制剂联合其他药物

2.1 PARP抑制剂联合抗血管生成药物

血管生成是肿瘤生长和转移过程中不可或缺的一环,抑制肿瘤血管生成,可使肿瘤细胞因缺乏生存所必需的氧气和营养而死亡,而缺氧本身与HRR功能受损有关^[8-10]。在使用PARP抑制剂治疗的过程中,由于*BRCA*基因的继发性突变使得HRR功能恢复,从而导致肿瘤细胞对PARP抑制剂耐药^[11]。在*BRCA2*基因继发性耐药突变的背景下,血管内皮生长因子受体3抑制剂可通过抑制*BRCA1*和*BRCA2*基因的表达来恢复人卵巢癌细胞对PARP抑制剂的敏感性^[11]。在鼠类肉瘤病毒癌基因突变型结直肠癌动物模型中,研究者通过联合使用血管内皮生长因子抑制剂贝伐珠单抗与奥拉帕利进行干预后发现,联合干预能够有效地抑制肿瘤细胞生长,其作用机制与贝伐珠单抗致肿瘤微环境内乏氧水平升高和HRR功能受损有关^[12]。Kaplan等^[13]在无*BRCA*基因缺失的人乳腺癌和人卵巢癌细胞中发现,一方面,抗血管生成药物西地尼布可诱导缺氧,从而抑制*BRCA*和Rad51的表达;另一方面,西地尼布可直接作用于HRR而不依赖肿瘤细胞的乏氧状态,这种直接作用可能与抑制血小板源性生长因子受体、激活蛋白磷酸酶2A、抑制E2F4转录因子介导的*BRCA*和Rad51表达有关。

2.2 PARP抑制剂联合热休克蛋白90抑制剂

热休克蛋白90(heat shock protein 90, HSP90)是一种腺苷三磷酸(adenosine triphosphate, ATP)依赖性分子,可以与*BRCA1*、*BRCA2*基因和细胞周期检查点激酶1(checkpoint kinase 1, CHK1)、Rad51、减数分裂重组11蛋白等相互作用,进而影响细胞DNA损伤的修复和细胞周期的调节^[14-15]。可见,HSP90抑制剂可通过影响HRR和非同源末端连接功能来抑制DNA双链的损伤修复,联合PARP抑制剂可对恶性肿瘤细胞产生合成致死作用^[14]。Lin等^[16]合成了一系列可抑制HSP90的新化合物,发现这些新化合物可抑制人乳腺癌和人胰腺癌细胞的增殖,且联合PARP抑制剂具有更强的细胞毒性作用。Gabbasov等^[17]发现,HSP90抑制剂Ganetespib可增强非*BRCA*基因突变的人卵巢癌细胞对PARP抑制剂Talazoparib的敏感性,且Ganetespib对DNA修复和细胞周期检查点相关蛋白表达的抑制作用呈剂量和时间依赖性。

2.3 PARP抑制剂联合磷脂酰肌醇3-激酶/蛋白激酶B/哺乳动物雷帕霉素靶蛋白抑制剂

磷脂酰肌醇3-激酶/蛋白激酶B/哺乳动物雷帕霉素靶蛋白(phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin, PI3K/AKT/mTOR)是细胞内的重要信号通路之一,可参与细胞周期调控、增殖、凋亡和糖原代谢等^[18]。据报道,在人子宫内膜癌细胞中,抑制PI3K的表达可下调*BRCA1*、*BRCA2*基因的表达,诱导肿瘤细胞HRR功能受损,从而增强子宫内膜癌细胞对PARP抑制剂奥拉帕利的敏感性^[19]。研究表明,联合使用PI3K抑制剂BKM120和奥拉帕利能够显著抑制人胃癌细胞增殖,诱导细胞凋亡和DNA损伤,其作用可能与胃癌细胞中缺乏的染色质重塑基因*ARID1A*有关^[20]。Bian等^[21]发现,*PTEN*基因缺失的子宫内膜癌细胞对奥拉帕利并不敏感,而当奥拉帕利与BKM120联用后,前者对肿瘤细胞的敏感性有所增加,其相关机制为BKM120可下调Rad51和*BRCA1*的表达,抑制HRR功能并诱导DNA损伤累积。De等^[22]发现,PI3K与mTOR双重抑制剂GDC-0980可抑制人三阴性乳腺癌细胞DNA损伤的修复,GDC-0980联合Veliparib、卡铂可抑制裸鼠体内移植瘤的生长,其作用机制与Ki67、CD31、磷酸化的血管内皮生长因子受体表达降低有关。

2.4 PARP抑制剂联合丝裂原活化的细胞外信号调节蛋白激酶抑制剂

丝裂原活化的细胞外信号调节蛋白激酶(mitogen-activated extracellular signal-regulated kinase, MEK)属于有丝分裂原激活的蛋白激酶信号通路的一部分,对细胞凋亡、细胞周期调控、细胞增殖和迁移等具有重要作用^[23]。Sun等^[24]研究发现,与单用药相比,PARP抑制剂与MEK抑制剂联用对*RAS*基因突变相关肿瘤具有更强

的抑制作用,其作用机制主要包括以下几点:(1)可通过下调B细胞淋巴瘤2(B cell lymphoma 2, Bcl-2)的表达来促进细胞凋亡;(2)可抑制HRR功能,从而诱导DNA损伤累积;(3)可抑制DNA损伤检查点相关蛋白的表达;(4)可通过诱导缺氧来降低血管密度,从而增强肿瘤细胞对PARP抑制剂的敏感性。Ethier等^[23]发现,在人宫颈癌HeLa细胞中,PARP抑制剂PJ34联合MEK抑制剂U0126可增强甲基硝基亚硝基胍的细胞毒性作用,其机制可能与抑制MEK/细胞外信号调节激酶(extracellular-signal regulated protein kinase, ERK)通路诱导的细胞凋亡有关。

2.5 PARP抑制剂与ATR、CHK1和WEE1抑制剂联用

抑制ATR/CHK1/WEE1信号轴可影响HRR功能,破坏复制叉的稳定性^[25]。ATR抑制剂可在DNA修复时干扰*BRC A2*和Rad51的募集,重构同源重组缺陷状态,增强DNA损伤类药物对肿瘤细胞的杀伤性^[25-26]。Kim等^[27]对PARP抑制剂和铂类双重耐药型人卵巢癌细胞进行研究,发现奥拉帕利联合ATR抑制剂AZD6738具有协同抗肿瘤作用,且与复制叉堆积、DNA双链损伤和细胞凋亡有关。Southgate等^[28]以ATR抑制剂VE-821和奥拉帕利联合处理人高危神经母细胞瘤,发现两者联合增强了H2AX^{S129}的表达,抑制了奥拉帕利致Rad51焦点的形成,从而增强了高危神经母细胞瘤对奥拉帕利的敏感性。Burgess等^[29]对PARP抑制剂敏感型和耐药型胚系*BRC A1*基因突变人卵巢癌细胞进行研究,发现奥拉帕利联合VE-821对两种人卵巢癌细胞均表现出协同抗肿瘤作用,其协同评分高于奥拉帕利与CHK1抑制剂MK-8776联用。在*ATM*缺失型人肺癌细胞中,奥拉帕利单用对细胞活性并无明显影响,而联用VE-821会产生细胞毒性作用,这种作用与两者将细胞周期阻滞在G₂期有关^[30]。在人黑色素瘤细胞中,奥拉帕利联合ATR抑制剂AZD6738同样具有协同抗肿瘤效果^[31]。Schoonen等^[32]在基于*BRC A2*基因缺失的人宫颈癌HeLa细胞的研究中发现,ATR抑制剂可诱导细胞过早地进行有丝分裂,导致染色质桥形成和染色体滞后,从而增强肿瘤细胞对奥拉帕利的敏感性,其协同作用与基因组不稳定性、环状鸟苷一磷酸-腺苷一磷酸合成酶/干扰素基因刺激因子(cyclic GMP-AMP synthase/stimulator of interferon genes, cGAS/STING)介导的炎症信号通路有关。

在*BRC A*突变型和野生型人卵巢癌细胞中,抑制ATR下游效应蛋白CHK1的表达已被证实可协同PARP抑制剂发挥抗肿瘤作用^[33-34]。Kim等^[33]以人源性卵巢癌异种移植瘤为模型进行研究,发现PARP抑制剂单用可抑制肿瘤细胞增殖,但最大可耐受剂量却不能抑制裸鼠移植瘤的生长,其原因可能与PARP抑制剂通过上调磷酸化ATR和CHK1的表达来破坏基因组稳定性有关。该研究分别将ATR抑制剂、CHK1抑制剂与PARP抑制

剂联合使用,发现联用可将肿瘤细胞从G₂期释放出来,使其提前进入有丝分裂进而导致染色体畸变和细胞凋亡增加,从而使肿瘤细胞的生长受到明显抑制。Brill等^[34]以奥拉帕利和CHK1抑制剂Prexasertib联合处理人高级别浆液性卵巢癌细胞系,发现与对照组或单药组相比,两药联用具有更强的抑癌活性,其作用可能与Prexasertib可消除奥拉帕利所导致的Rad51表达上调有关。Smith等^[35]通过对*BRC A2*突变型V-C8细胞和*BRC A2*野生型V-C8.B2细胞进行研究,发现V-C8细胞对PARP抑制剂Rucaparib具有更强的敏感性;而对于本不敏感的V-C8.B2细胞,联用CHK1抑制剂PF-477736可增强V-C8.B2细胞对Rucaparib的敏感性。

Jin等^[36]对人三阴性乳腺癌细胞进行研究,发现WEE1抑制剂AZD1775联合ATR抑制剂AZD6738具有更强的抗肿瘤活性,其协同作用机制与DNA损伤累积有关;此外,WEE1与ATR的双重抑制使Rad51表达下调,增强了肿瘤细胞对顺铂和PARP抑制剂的敏感性。

2.6 PARP抑制剂联合溴结构域和超末端结构域/溴结构域蛋白4抑制剂

溴结构域和超末端结构域(bromodomain and extra-terminal, BET)蛋白家族对细胞生长和细胞周期具有重要的调控作用,溴结构域蛋白4(bromodomain-containing protein 4, BRD4)属于BET蛋白家族成员之一,可通过调控*MYC*、*CDK*、*BCL2*等下游基因来影响肿瘤的发生与发展^[37]。Miller等^[38]研究发现,BET抑制剂JQ-1可诱导DNA损伤标志物 γ H2AX的高表达,同时抑制DNA损伤修复蛋白Ku80和Rad51的表达;与单药相比,JQ-1联合PARP抑制剂奥拉帕利对胰腺癌小鼠移植瘤表现出更强的抑癌作用,其作用与Ku80、Rad51表达受到抑制有关,而Ku80、Rad51的表达受BRD4、BRD2调控。在去势耐药性前列腺癌动物模型中,BET抑制剂联合PARP抑制剂也表现出了协同抗肿瘤作用^[39]。在*BRC A*野生型人卵巢癌细胞中,BET抑制剂JQ-1可下调G₂/M期细胞周期检查点调节因子WEE1和DNA损伤反应因子TOPBP1的表达;当JQ-1与奥拉帕利联用时,可使肿瘤细胞在DNA损伤累积的情况下进入有丝分裂,从而导致有丝分裂障碍和细胞死亡,该协同作用效果在动物实验中得到了验证^[40]。在小细胞肺癌动物模型中,PARP抑制剂联合BET抑制剂可通过靶向MYC/PARP1轴发挥抗肿瘤作用^[41]。

2.7 PARP抑制剂联合细胞周期蛋白依赖性激酶12抑制剂

细胞周期蛋白依赖性激酶12(cyclin-dependent kinase 12, CDK12)属于丝氨酸/苏氨酸蛋白激酶家族,可调节基因转录、DNA损伤反应以及细胞增殖和分化等^[42]。尽管PARP抑制剂对于HRR功能缺失的肿瘤细胞是有效的,但该功能恢复所导致的获得性耐药极大限制

了PARP抑制剂的使用^[43]。Johnson等^[43]发现,在BRCA突变型人三阴性乳腺癌细胞和人源异种移植瘤中,CDK12抑制剂Dinaciclib可呈时间和剂量依赖性地抑制BRCA1和Rad51的表达,与Veliparib联用后可协同抑制乳腺癌细胞和裸鼠移植瘤的生长。Joshi等^[44]发现,在卵巢癌细胞中,敲除CDK12基因可以抑制BRCA1基因的表达,导致HRR功能丧失,从而增强卵巢癌细胞对Veliparib和顺铂的敏感性。

2.8 PARP抑制剂联合免疫检查点抑制剂

肿瘤的发生发展与人体免疫功能失常密切相关,免疫检查点在正常情况下可抑制T细胞功能,但在肿瘤组织中却可被利用而形成免疫逃逸^[45]。目前,研究者发现的免疫检查点包括程序性死亡蛋白-1(programmed-death protein-1,PD-1)、细胞毒性T淋巴细胞相关抗原4和程序性死亡蛋白配体-1(programmed death ligand-1,PD-L1)^[45]。通过免疫检查点抑制剂可抑制上述分子的活性,激活T细胞对肿瘤的免疫应答反应,从而发挥抗肿瘤作用。在人结肠癌、人肺鳞状细胞癌、人乳腺癌、人肉瘤和人膀胱癌细胞中,Wang等^[46]发现,尼拉帕利联合PD-1抑制剂可增加免疫细胞的浸润并延缓肿瘤细胞的生长,这种联用效果与BRCA的基因分型无关。Ding等^[47]发现,在BRCA1缺失卵巢癌小鼠中,奥拉帕利可触发其局部和全身的抗肿瘤免疫反应,激活STING通路并上调PD-L1的表达;而当奥拉帕利与PD-1抑制剂联用时,这种免疫触发效果进一步增强,使裸鼠体内肿瘤细胞的生长受到更强的抑制,小鼠生存期得以明显延长。

2.9 PARP抑制剂联合组蛋白脱乙酰酶抑制剂

组蛋白脱乙酰酶(histone deacetylases,HDAC)在DNA双链损伤修复中具有重要作用^[48]。Wiegman等^[48]分别研究了3种HDAC抑制剂SAHA、VPA、ROMI对人三阴性乳腺癌细胞的抑制作用,发现SAHA和ROMI可抑制细胞的HRR功能,使Rad51、BRAD1和FANCD2基因的表达显著下调,从而与PARP抑制剂Veliparib产生合成致死作用。在人卵巢癌细胞中,奥拉帕利联合HDAC抑制剂SAHA可通过靶向HRR功能来发挥协同抑癌作用^[49]。Yin等^[50]以人前列腺癌细胞为对象,发现Veliparib协同SAHA可抑制细胞增殖,诱导细胞凋亡和DNA损伤,而对正常前列腺上皮细胞RWPE-1没有影响,其协同作用可能与靶向泛素样含PHD和环指域1(ubiquitin-like PHD and ring finger domains 1,UHRF1)/BRCA1蛋白复合物、抑制BRCA1的表达有关;此外,Rad51基因沉默可增强前列腺癌细胞对SAHA和奥拉帕利联用的敏感性。Liang等^[51]以人肝癌细胞为研究对象,发现PARP抑制剂PJ34联合SAHA可抑制细胞增殖,诱导细胞凋亡,抑制裸鼠移植瘤的生长。Baldan等^[52]对人间变性甲状腺癌进行的研究结果显示,SAHA与PJ34联用可发挥协同抗肿瘤作用,其协同作用可能与上调

TSHR基因的表达有关。Hegde等^[53]研究了新型PARP抑制剂P10联合SAHA对白血病细胞的作用,发现P10可协同SAHA诱发内源性凋亡途径,引起DNA损伤和S期细胞周期阻滞,从而发挥协同抗癌作用。

2.10 PARP抑制剂与中药单体联用

近年来,天然产物由于毒性小、安全性高等优势,在治疗恶性肿瘤领域受到了越来越多学者的关注。Hou等^[54]以人卵巢癌细胞为研究对象,发现小檗碱可诱导DNA氧化损伤并抑制HRR功能,与尼拉帕利联用可发挥协同抗肿瘤作用,这种作用与小檗碱抑制Rad51表达和激活PARP,从而使卵巢癌细胞对尼拉帕利更加敏感有关。Wang等^[55]在研究土木香内酯(alantolactone,ATL)与PARP抑制剂的协同抗肿瘤作用时发现,人前列腺癌PC-3细胞会对非细胞毒性剂量(10 μmol/L)的ATL产生耐药性,这可能与激活DNA损伤修复蛋白PARP的表达有关;而非细胞毒性剂量的ATL联合非细胞毒性剂量(10 μmol/L)的奥拉帕利可对肿瘤细胞产生致死作用,对包括人前列腺癌、人肺癌和人结肠直肠癌等多种肿瘤细胞均展现出广谱抗癌作用,这种作用与ATL诱导的DNA氧化损伤和PARP抑制剂形成的PARP捕获直接相关。

除上述研究外,在人结肠癌细胞体内外实验中,PARP抑制剂联合糖原合成酶激酶3β(glycogen synthase kinase-3β,GSK3β)抑制剂具有明显的协同作用,GSK3β抑制剂可通过下调BRCA1的表达而抑制HRR功能,使结肠癌细胞对PARP抑制剂更加敏感^[56]。

3 结语

PARP抑制剂对于HRR功能缺陷的肿瘤细胞具有独特的细胞毒性作用。然而,并不是所有HRR功能缺陷的肿瘤细胞均对PARP抑制剂敏感,部分肿瘤细胞还会产生获得性耐药^[57]。可见,寻求具有增敏增效或克服耐药效果的PARP抑制剂与其他药物的联合干预方案显得尤为重要。近年来,越来越多的研究聚焦在PARP抑制剂与放疗或者化疗等药物的联合治疗上,研究结果显示,联合干预既可以减轻药物的不良反应,又能提高药物的干预效果。随着研究的不断深入,PARP抑制剂联合其他药物所产生的诸多问题和困惑也有待进一步探索与理清。因此,笔者认为后续研究方向可从以下几个方面展开:(1)关于药物长期使用的安全性问题,尽管PARP抑制剂的主要作用基础为肿瘤细胞DNA损伤,但在长期使用的环境下,药物是否会对人体正常组织和功能产生影响、其安全性能否得到保障还有待检验。(2)关于PARP抑制剂联合治疗的使用剂量问题,一方面需要确定化疗药物的适宜剂量,确保患者在可耐受的情况下获得较好的疗效;另一方面,作为放疗增敏剂的PARP抑制剂使用剂量也需要慎重考察。(3)关于PARP抑制剂治疗的耐药性问题,包括HRR相关基因的二次突变、

HRR 与非同源末端连接的失衡以及复制叉的保护作用等^[57-59]。通过上述联合用药研究结果来看,PARP 抑制剂与放疗或其他药物的结合或许可以克服这种局限。通过相关的临床试验,比如定期进行液体活检取样等,及时发现耐药机制并优化靶向药物组合依然是十分必要的^[59]。相信随着研究的不断深入,会有更多安全且有效的 PARP 抑制剂联合干预方案得以应用,从而使更多的患者获益。

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