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综述

铂类抗癌药物作用靶点及耐药机制的研究进展

李银燕 王秀君*

(浙江大学医学院药理学系, 杭州 310058)

摘要 顺铂、卡铂、奥沙利铂这一类铂类抗癌药物在治疗卵巢癌、宫颈癌、肺癌、结肠癌、淋巴癌等癌症中起重要作用。铂类抗癌药物进入细胞核, 作用于DNA分子后, 形成Pt-DNA化合物, 导致DNA结构改变, DNA复制转录障碍, 引起细胞凋亡。由于激活细胞内一些信号通路, 引起耐药与毒性。该文综述了顺铂、卡铂和奥沙利铂的临床应用、作用靶点、毒性和耐药机制的最新研究进展, 将为优化铂类抗癌药物的治疗方案提供理论依据。

关键词 铂类抗癌药物; 化学治疗; 耐药机制; 毒性

Molecular Mechanisms of Chemoresistance and Cytotoxicity Associated with Platinum Drugs

Li Yinyan, Wang Xiujun*

(*Department of Pharmacology, College of Medicine, Zhejiang University, Hangzhou 310058, China*)

Abstract Cisplatin, carboplatin and oxaliplatin have been used clinically for treatment of many types of cancers, including ovarian, cervical, lung, colorectal cancer and relapsed lymphoma. Platinum-DNA adducts are formed following the uptake of the drug into the cell nucleus. As a result, DNA structure is changed, leading to the disorder of DNA replication and transcription, and eventually the cell death. Treatment with platinum agents is characterized by resistance and toxicity through activating a number of signal transduction pathways. This article highlights recent discoveries in cellular pathways responsive to the platinum agents, and provides a molecular basis for understanding the differences in clinical application, cytotoxicity and drug resistance among the platinum anticancer drugs.

Key words platinum agents; chemotherapy; drug resistance; cytotoxicity

铂类抗癌药物, 主要指顺铂、卡铂、奥沙利铂, 是目前临床应用中对多种癌症具有较高活性的抗癌药物。顺铂(cisplatin)自从上世纪70年代被发现可以抑制肿瘤细胞生长后, 就广泛应用于癌症化学治疗, 在化疗药物中占有重要的位置[1]。顺铂临床应用已经超过30多年, 与博来霉素(bleomycin)、依托泊苷(etoposide)联用治疗睾丸癌效果显著。第二代铂类抗癌药物卡铂(carboplatin)与顺铂结构极其相似(图1A), 其作用机理和耐药方面也有共同点, 两者皆用于治疗卵巢癌、非小细胞肺癌、头颈癌、宫颈癌、

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*通讯作者。Tel: 0571-88208500, E-mail: xjwang@zju.edu.cn

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*Corresponding author. Tel: +86-571-88208500, E-mail: xjwang@zju.edu.cn

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淋巴癌等, 但因为毒性和耐药性限制了顺铂、卡铂的使用范围。奥沙利铂(oxaliplatin)是第三代铂类抗癌药, 其疗效好、毒性小, 而且与顺铂、卡铂无交叉耐药, 特别是在治疗结肠癌、肺癌、乳腺癌方面均有较好的治疗效果[2]。本文基于目前已有的研究结果, 重点介绍铂类抗癌药物临床应用、作用靶点、毒副作用及耐药机理。

1 铂类抗癌药物的临床应用

顺铂具有抗癌谱广、作用强、与多种抗肿瘤药有协同作用等特点, 在治疗肺癌、卵巢癌、膀胱癌、睾丸癌、头颈癌、食道癌、胃癌等方面作为一线药物, 特别是睾丸癌早期治愈率达100%、卵巢癌早期治愈率达80%以上[1]。Serša等[1]对133位黑色素瘤患者临床观察发现, 顺铂联合电化学疗法对治疗黑色素瘤效果显著, 不仅操作简单、周期短、顺铂剂量低而且副作用小。在治疗肺癌方面, 顺铂联合吉西他滨(gemcitabine)可作为治疗非小细胞肺癌的一线药物, 联合培美曲塞(pemetrexed)在临床II期也有不错的治疗效果[3]。最新的中国临床试验发现, 这两种治疗非小细胞肺癌的方法都有一定的效果, 但培美曲塞联合顺铂效果相对更好, 同时安全性也更好[4]。Vogelzang等[5]在III期临床研究治疗恶性胸膜间皮瘤中发现, 顺铂联用培美曲塞, 同时补充维生素B_{12}和叶酸能明显提高存活率, 减少顺铂引起的毒副作用。另外, 顺铂联合放疗治疗宫颈癌也有很好的治疗效果。研究发现, DD(dose-dense)药物治疗方法, 即采有低剂量顺铂与低剂量紫杉醇联合治疗可对抗癌症的复发[6]。

卡铂的抗癌谱与顺铂类似, 在研究卡铂和顺铂分别治疗非小细胞肺癌疗效的实验中发现, 两者在存活率上没有发现显著的差别[7]。单用卡铂对非小细胞肺癌治愈率达60%[8]。卡铂联合依托泊苷(etoposide)与顺铂联合伊立替康(irinotecan)交替使用一周对治疗各个阶段的非小细胞肺癌均有较好疗效[9]。另有研究发现, 卡铂联合紫杉醇对非小细胞肺癌年长患者治疗安全有效[10]。

奥沙利铂显著的临床优势在于单独或者与5-FU(5-fluorouracil)、亚叶酸联合应用治疗转移性结直肠癌。在顺铂等一些抗癌药物对结肠癌没有良好治愈率的情况下, 从最初的I期临床试验成功后, 世界上许多国家开始应用奥沙利铂治疗结肠癌。因为奥沙利铂单独给药, 对很多癌症效果不显著, 因而奥沙利铂多与其他药物联用。有临床研究发现奥沙利铂、顺铂、紫杉醇(paclitaxel)三者联用可以有效治疗卵巢癌[11], 与5-FU、卡培他滨(capecitabine)联合用药能有效治疗结肠癌[12]。辅助疗法在治疗III期结肠癌切除病人时, 采用贝伐单抗(bevacizumab)辅助奥沙利铂治疗时, 没有明显延长存活期, 故该治疗方案效果不理想[13]。奥沙利铂联合卡培他滨治疗高龄晚期贲门癌患者, 改善症状快, 不良反应患者可以耐受[14]。

铂类抗癌药物因为存在剂量限制, 多与其他药物联用。最近研究发现, 奥沙利铂、顺铂、卡铂对细胞色素P450(cytochrome P450)几乎没有抑制作用, 这也说明这几类药物与其他药物可以进行联用[15]。表1是从美国国立卫生院(NIH)的临床试验网站(http://www.clinicaltrails.gov)得到的目前已完成或正在进行的铂类抗癌药物与其他药物联用的临床试验数据, 结果表明联用其他药物对改善铂类药物临床疗效起了很大作用。

随着分子靶向药物的问世, 多种靶向药物已在临床上和铂类抗癌药物联合应用, 并取得了不错的疗效。赫赛汀(herceptin)是重组DNA衍生的人源化单克隆抗体, 选择性作用于HER-2蛋白, 氟尿嘧啶和顺铂联合赫赛汀一线治疗晚期胃癌三药方案疗效优于氟尿嘧啶联合顺铂的两药方案[16]。利妥昔单抗(rituximab)是针对CD20的人/鼠嵌合单抗, 可用于治疗低度恶性淋巴瘤。地塞米松、大剂量阿糖胞苷、奥沙利铂联合或不联合利妥昔单抗用于治疗复发和难治性非霍奇金淋巴瘤[17]。贝伐单抗为新型抗血管内皮生长因子受体(vascular endothelial growth factor, VEGF)的人源化单抗, 单用卡铂对非小细胞肺癌治愈率达60%以上, 联合贝伐单抗治疗非小细胞肺癌存活率明显增加[8]。西妥昔单抗(cetuximab)是一种针对表皮生长因子受体(epidermal growth factor receptor, EGFR)的单克隆抗体, 西妥昔单抗与EGFR结合能阻断肿瘤细胞信号传导, 促进受体降解。分子靶向药物盐酸厄洛替尼片(tarceva)抗肿瘤的作用机制主要为抑制EGFR酪氨酸激酶胞内磷酸化, 吉非替尼(gefitinib)的作用机制主要是通过抑制EGFR自身磷酸化而阻滞传导, 抑制肿瘤细胞的增殖, 实现靶向治疗, 这两种药物与顺铂联用都可有效治疗中晚期肺癌患者[18]。此外, 还有多靶点药物索

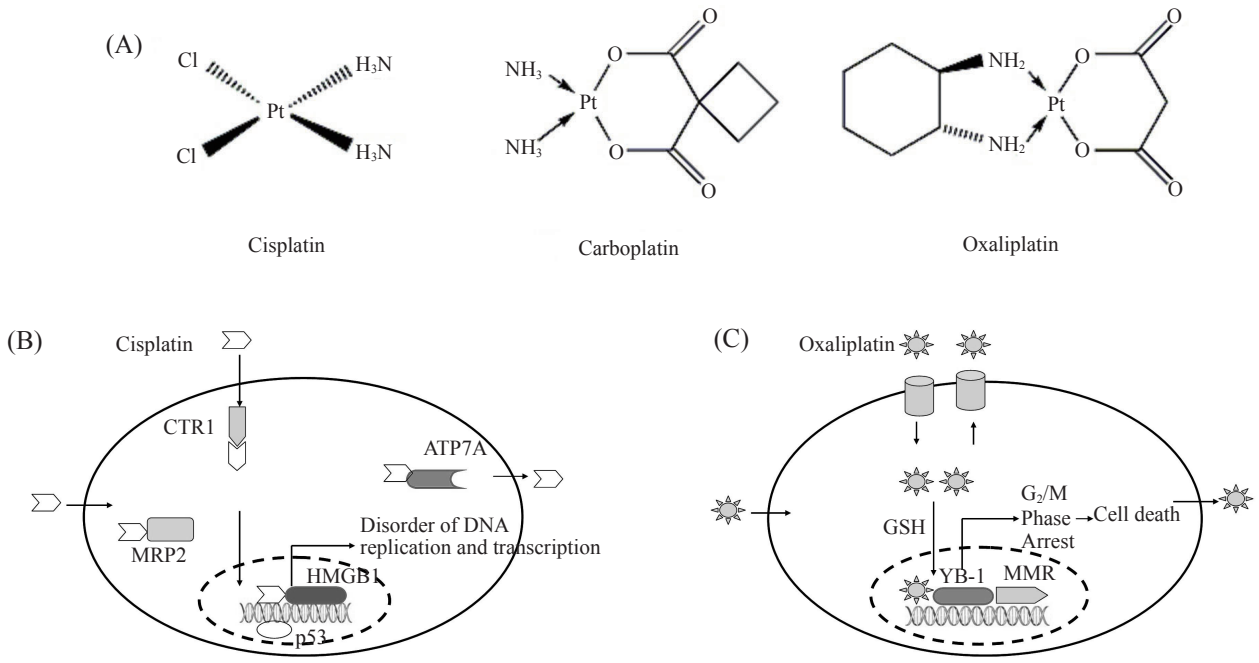

图1 顺铂、卡铂、奥沙利铂的化学结构及顺铂、奥沙利铂在细胞内的作用通路

Fig.1 The chemical structures of cisplatin, transplatin, oxaliplatin and mechanisms of their actions

表1 顺铂、卡铂、奥沙利铂的临床试验

Table 1 Clinical trails for platinum-based combination

铂类抗癌药物 Platinum	临床联合治疗药物 Drugs in combination therapy	治疗疾病 Disease	项目编号 Identifier
Cisplatin	Irinotecan	Gastrointestinal cancer (Phase II trails)	NCT00353015[a]
	Cediranib, Capecitabine	Lung cancer (Phase I trails)	NCT00960349[a]
	Topotecan	Small cell lung cancer (Phase Ⅲ trails)	NCT00320359[a]
	Afatinib, Paclitaxel, 5-FU	Cancer (Phase I trails)	NCT00716417[a]
Transplatin	Paclitaxel	Peritoneal cancer (Phase I trails)	NCT00085358[a]
	CDP791	Non squamous non-small cell cancer (Phase II trails)	NCT00152477[a]
	BIIB022, Paclitaxel	Small cell lung cancer (Phase I trails)	NCT00970580[a]
	Trastuzumab, Ixabepilone	Breast cancer (Phase II trails)	NCT00077376[a]
Oxaliplatin	Capecitabine	Colorectal cancer (Phase II trails)	NCT00677144[a]
	Bevacizumab, Capecitabine	Gastrointestinal cancer (Phase II trails)	NCT01061515[b]
	5-FU, Leucovorin	Lung cancer (Phase II trails)	NCT00447967[a]
	ON 01910.Na	Liver cancer (Phase I trails)	NCT00861783[c]
	Fludarabine, Cytarabine, Rituximab	Leukaemia (Phase I, II trails)	NCT00452374[a]
	Gemcitabine, Erlotinib	Pancreatic cancer, Bile duct cancer (Phase I trails)	NCT00266097[a]

Information from http://www.clinicaltrails.gov; [a]completed, [b]recruiting, [c]uncompleted.

拉菲(sorafenib)等与铂类联合治疗肝癌患者[19]。

2 铂类抗癌药物作用靶点

铂类抗癌药物进入细胞后, 解离失去酸根负离子, 如氯离子或者草酸根离子, 同时结合两分子的水, 形成带正电荷的水合铂。这个带正电荷的水合铂可以跟细胞内亲质子的分子结合, 包括DNA、RNA和蛋白质。铂原子选择性地与DNA分子中的鸟嘌呤和腺嘌呤上的N7原子结合, 形成3种不同结构的复合物, 即单加合物、链内配对交联、链间配对交联, 但几乎大部分结构都是链内配对交联, 即1,2-d(GpG)交联。所有的交联都会使DNA发生扭转,

从而破坏DNA的结构[20]。

2.1 顺铂、卡铂作用靶点

顺铂通过被动扩散或者通过转运子(copper transport protein 1, CTR1)运输进入细胞质, 再进入细胞核作用于DNA分子。顺铂与DNA模板链形成的1,2-d(GpG)、1,3-d(GpTpG)阻碍T7 RNA聚合酶的结合, 这个细胞内信号的阻断使得细胞发出细胞受损信号启动凋亡[21]。HMG(high mobility group)是一个由80个氨基酸组成的蛋白, 可以识别并且结合到DNA上, 与1,2-d(GpG)形成交联。HMGB1(high-mobility group box 1 protein)是HMG的家族成员, 研究发现, 顺铂可以诱导HMGB1与DNA上的1,2-d(GpG)结合, 形成顺铂-DNA-HMGB1复合体, 从而阻碍DNA的复制与转录[22]。睾丸组织对顺铂和卡铂的敏感性特别强, 很可能就是因为有多个HMG蛋白的表达[22]。HMGB1与p53互为激活剂, p53为癌症抑制因子, 通过免疫共沉淀的实验发现, 在DNA损伤后, HMGB1与p53两者存在相互作用, 共同结合到DNA上, 启动p53介导的DNA修复。错配修复蛋白Muts参与顺铂引起的DNA修复, 可特异性识别顺铂-DNA复合物, 两倍高于奥沙利铂-DNA复合物, 在Muts突变的细胞内, 顺铂药效明显增强[23]。组蛋白的修饰可以改变染色体的结构, 促进转录、复制等相关核因子的结合。研究发现, 顺铂通过诱导p38 MAPK(mitogen-activated protein kinase)通路, 磷酸化组蛋白H3的Ser-10, 乙酰化组蛋白H4[24]。顺铂和卡铂作用于细胞后, 激活细胞内的信号通路, 例如p38、MAPK、JNK(c-Jun N-terminal kinase)、ERK(extracellular signal-regulated protein kinase)[25]信号通路调节转录因子, 从而影响基因的表达情况(图1B)。

卡铂与顺铂主要作用靶点类似, 两者的差别在于形成Pt-DNA化合物的速率不同, 因而卡铂治疗效果稍弱, 毒性也更小。卡铂与DNA形成六原环, 表现出更好的水溶性和稳定性, 卡铂的药物代谢需要两步反应, 首先是六元环的开环, 这是一个限速且关键的步骤, 后一步是配基的解离, 这一步相对较快[26]。研究发现, 宫颈癌细胞在卡铂作用下, 用抑制剂抑制*p53*或者使*p53*突变, 导致ERK激活减少, 从而诱导细胞凋亡[27]。

2.2 奥沙利铂作用靶点

奥沙利铂与顺铂、卡铂化学结构差别在于奥沙利铂(图1A)带有一个1,2-二氨基环己烷基团(diaminocyclohexane ligand, DACH), 铂原子与DNA形成体积较大的Pt-DNA化合物(图1C), 导致DNA更难修复和复制受阻, 诱导更多细胞凋亡[20]。正因为形成体积较大的Pt-DNA化合物, 研究发现, 与顺铂等摩尔的奥沙利铂形成的链间交联更少[28], HMG对奥沙利铂的亲和力也较顺铂和卡铂低[22]。转录因子YB-1(Y-box binding protein)可结合到奥沙利铂形成的Pt-DNA复合物上[29]。在与顺铂等浓度条件下, 顺铂主要是减慢了复制的速率, 激活了G_2-M阶段, 而奥沙利铂主要激活了G_1-S阶段, 阻断了G_2-M的阶段。研究发现, 与奥沙利铂调控相关的117个基因中, 有79个与顺铂起相同的作用, 剩余的38个基因则是奥沙利铂剂量依赖被抑制的。相反地, 顺铂对这38个基因是无关或者剂量依赖增加的, 而与细胞周期相关的CDK1、cyclin B蛋白就属于38个基因当中被调控的, 这就可以解释两者作用机理不同的原因[30]。同时其他的研究发现, 奥沙利铂影响钠离子与钙离子交换通道, 是引起神经毒性的一个重要原因[31]。更多具体的顺铂、卡铂、奥沙利铂作用靶点见表2。

3 铂类抗癌药物的毒性

铂类抗癌药物对机体产生毒性的原因主要是由于铂原子与DNA形成的化合物, 顺铂、卡铂、奥沙利铂毒性的不同与化合物的结构有关。顺铂和奥沙利铂结合在DNA上的同一个位点, 但是两种化合物在结构上有很大的差别, 最终形成的DNA复合物被细胞内特定蛋白识别的能力有所不同[20]。例如, 错配修复蛋白和损伤蛋白识别两种化合物能力的不同, 导致亲和力不同, 这就是两者引起不同毒性的原因之一[20]。顺铂、卡铂、奥沙利铂引起的主要毒性见表3。

顺铂引起的主要毒性是肾毒性。研究发现, 对12个病人注射正常剂量的顺铂, 2周后就会出现肾脏功能障碍, 随着注射时间、注射剂量会有累加的效果, 12至24个月会出现严重肾毒性, 肾小球滤过率和有效肾血浆流量减少23%和19%, 年长患者情况尤其严重[35]。临床上还伴有低镁症、低钾症等其他症状。可以通过含氯化物的注射液或者其他电解液来缓解症状, 例如氨磷汀, 已被广泛应用于临床减轻顺铂引起的肾毒性, 而不影响化疗效果[35]。此外, 顺铂对胃肠道、神经系统、血液系统、视觉、肝、心血

管、皮肤系统及代谢系统都有毒副作用[36]。最新对肝癌细胞的研究发现, 顺铂激活MKK/ERK通路, 影响BH3-only凋亡蛋白, 同时发现*ERK1*沉默后明显减弱顺铂引起的毒性[37]。

卡铂由于其骨髓抑制作用而限制了使用范围, 病人往往在使用卡铂的同时, 伴有严重的骨髓抑制, 出现贫血症, 随着剂量增加, 情况也会变得更加严重[38]。当卡铂与其他骨髓抑制药物联用或者同时放疗时, 会加重其副作用。此外, 卡铂对胃肠道、神经系统、肝、代谢系统也有毒副作用[39]。

奥沙利铂对周围神经的毒性主要有两种: 急性和慢性, 两者跟用药时间长短有关。在临床I期实验中发现, 单独使用奥沙利铂会产生短暂的急性感觉迟钝, 多次使用会产生末梢神经中毒现象, 但在终止用药后情况会好转[12]。Misset等[12]首次报道, I期临床研究发现, 奥沙利铂配伍卡培他滨达到最大耐受剂量之后, 这一组13个病人给以详细的神经检查, 包括针极肌电图检查、神经传导研究, 对比给药前与给药后发现所有的病人都表现为急性、可逆转的神经毒性。症状包括感觉异常, 冷过敏, 注射过程中下巴、眼睛、手臂疼痛, 腿部抽筋, 视觉和声音的改变。针极肌电图检查和神经传导研究发现注射奥沙利铂后运动神经异常活跃。目前, 有实验结果表明奥沙利铂影响了钠离子与钙离子的交换, 与引起外周神经毒性有很大关系[31], 另有实验发现使用钠离子、钙离子的药物能达到在不影响奥沙利铂治疗效果的基础上, 缓解神经毒性[40]。此外, 奥沙利铂对血液系统、胃肠道系统也有一定的毒副作用。

4 铂类抗癌药物耐药机理

铂类药物经典的耐药机制包括三方面: (1)药物摄取减少, 药物泵出增加, 两者都会导致细胞内药物浓度减少; (2)谷胱甘肽(glutathione, GSH)和其他抗氧化物质对铂类抗癌药物的解毒作用, 谷胱甘肽是细胞内一种分子量小且大量存在的具有抗氧化和解毒作用的三肽, 谷胱甘肽可以和Pt形成Pt-GST, 阻碍Pt与DNA的结合, 使得细胞内解毒作用增强, 细胞出现耐药; (3)增强DNA修复或者增加耐受[49-50]。表4列举了

表2 铂类抗癌药物作用靶点

Table 2 The cellular targets of platinum anticancer drugs

铂类抗癌药物 Platinum	作用靶点 Drugs targets	分子机制 Molecular mechanism	模型 Model
Cisplatin	Transcription factor	Inhibition of T7 RNA polymerase	*Escherichia coli* BL21[21]
	DNA repairing	Induces the participation of mismatch repair protein Muts and HMGB1	*Escherichia coli* BL21[23]; cervical cancer cell line Hela[22]
	Cellular signal transduction	Promotes apoptosis factor p53 expression, and enhances HMGB1 combination to Pt-DNA	Rabbit[32]
	Translation	Induces histone H3, H4 posttranslational modification	Cervical cancer cell line Hela and breast cancer cell line MCF-7[24]
	Signaling pathway	Activiates p38, MAPK and ERK pathway and induces apoptosis	Cancer cell lines IMR90, HaCaT, Hela, A431, HN30, HN19, 293T, and Cos7[25]
Carboplatin	DNA	Combination with genomic DNA	Human bladder cancer cells[26]
	Signaling pathway	Induces apoptosis via p53, MEK/ERK pathway	Cervical cancer cell lines SiHa and CaSki[27]
Oxaliplatin	DNA replication	Induces G_2/M phase; Inhibits the expression of cell cycle proteins CDK1 and cyclin B	Cervical cancer cell line HCT116[30,33];
	DNA repairing	Induces HMGB1 participation in formation of the Pt-DNA complex, and alters DNA transcription	Colorectal cancer cell line CT26[34]
	Translation	Induces transcription factor YB-1 participation in formation of the Pt-DNA complex	Colorectal cancer lines SW480 and HT29[29]
	Drug uptake	Affects sodium channel	Biopsies from in 22 cancer patients[31]

表3 铂类抗癌药物毒副作用

Table 3 Cytotoxicity of platinum anticancer drugs

铂类抗癌药物 Platinum	毒性 Cytotoxicity	模型 Model
Cisplatin	Renal cytotoxicity	Cancer cell line HEK293[35]; lymphoma patients[36]
	Peripheral nerve cytotoxicity	11 ovarian cancer patients[41]
	Gastrointestinal cytotoxicity	399 cancer patients[42]
Carboplatin	Hematologic cytotoxicity	31 cancer patients[38]
	Bone marrow suppression	Ovarian cancer patients[39]
	Visual impairment	Malignant glioma patients[43]
	Ototoxicity	Chinchilla[44]
Oxaliplatin	Peripheral nerve cytotoxicity	C57BL/6J mice[45]; cancer patients[46]
	Cryaesthesia	C57BL/6 mice[47]
	Gastrointestinal cytotoxicity	266 B6D2F1mice[48]

目前研究发现的顺铂、卡铂、奥沙利铂的耐药机制。

4.1 顺铂、卡铂耐药机理

顺铂治疗癌症一段时间后, 机体往往出现耐药现象, 使得治疗无效或者失败。对结肠癌和肾癌来说, 存在内源性耐药, 而其他类型的恶性肿瘤, 更多的是获得性耐药。研究发现, CTR1可以调节顺铂、卡铂、奥沙利铂运输进入细胞质, 在*CTR1*沉默的酵母细胞内这几类药物明显减少[51]。多药耐药蛋白(multidrug-resistance-associated-protein-2, MRP2)与顺铂耐药相关, 顺铂耐药的黑色素瘤细胞中MRP2的mRNA和蛋白水平明显增加, 核内Pt-DNA复合物明显减少, 可见MRP2蛋白对细胞本身的一个保护作用[52]。ATP7A(P-type adenosine triphosphate)具有代谢顺铂的功能, 人鳞状细胞癌KB3-1转染*ATP7A*后, 对顺铂和铜离子产生耐药[53]。抗凋亡程序在顺铂耐药细胞系中普遍被激活, A2780顺铂耐药细胞株中Bcl-2表达增加, 谷胱甘肽升高[54]。最新研究发现, Bim(Bcl-2 homology 3-only proapoptotic protein)受到ERK介导的磷酸化作用降解, 从而导致顺铂耐药[55]。Brozovic等[54]发现, caspase-8、caspase-9和caspase-3在顺铂耐药细胞系中被激活, SAPK/JNK(stressactivated protein kinase/c-Jun N-terminal kinase)信号通路和p38信号通路上调, 使细胞不能被诱导凋亡。核苷酸切除修复系统与顺铂耐药有很大关系。核苷酸切除修复分为: transcription-coupled NER(TC-NER)和global genome NER(GG-NER), 实验发现, TC-NER缺失的细胞对顺铂异常敏感, 而GG-NER对顺铂耐药影响不显著[56]。

卡铂耐药范围比顺铂要小, 但从两者作用机理来看, 就可知耐药机理也是非常相似, 因此常出现同时耐药。γ谷氨酰转移酶(γ-glutamyltransferase, GGT)通过增加细胞内GSH的水平来增强细胞对卡铂的解毒作用[57]。对63个早期卵巢癌进行比较基因组学研究发现, 卡铂的耐药与正常癌细胞基因组相比, 有明显的突变位点, 早期肿瘤与晚期肿瘤也存在差异[58]。Notch3高表达与低表达卵巢癌细胞系相比, 卡铂的IC_{50}明显增加, 这说明Notch3的异常表达使得卵巢癌耐药, 当卵巢癌细胞系OVCAR3降表达Notch3后可增加卡铂的药效[59]。

4.2 奥沙利铂耐药机制

奥沙利铂通过离子通道进入细胞质后, GSH可以与铂原子形成复合物, 降低奥沙利铂的活性。奥沙利铂和顺铂最大区别就在于没有交叉耐药, 有研究发现, MMR(mismatch repair)活性导致顺铂、卡铂内源性耐药。在人类基因中, 已经被发现有6种基因参与MMR过程, 分别是: *hMLH1*、*hMLH2*、*hPMS2*、*hMSH2*、*hMSH3*、*hMSH6*。*hMLH1*基因沉默导致蛋白表达缺失, 细胞识别DNA损伤的能力减弱, 细胞生长和增殖紊乱, 引起耐药。*MMR*基因上或者表观遗传上的改变都会影响整个系统的稳定性, 有可

表4 铂类抗癌药物的耐药机制

Table 4 Mechanisms of resistance to platinum anticancer drugs

铂类抗癌药物 Platinum	相关因子 Contributing factor	耐药机制 Mechanisms of resistance	模型 Model
Cisplatin	Decreased drug uptake	Ctr1 protein reduces the intracellular accumulation of cisplatin	Yeast, rat[51]; ovarian cancer cell line A2780[66]
	Increased efflux	Increased ATP7A expression Altered copper metabolic pathways Increased MRP2 levels	Human breast cancer cell lines[67]; skin cancer cell line KB-3-1[53]; melanoma cancer cell line MeWo[52]
	Increased detoxification	Increased GSH and metallothioneins	Cancer tissues[68]; ceivical cancer cell line Hela[57]
	Altered signal pathways	JNK, c-Jun, FasL and Fas pathway, and ERK mediated by MKP-1	Ovarian cancer cell lines 2008 and 2008C13[69]
	Increased tolerance of DNA adduct	Removal of cisplatin-DNA complex by TC-NER Depletion of MMR	Skin cancer cell line[56]; ceivical cancer cell line Hela[70]
	Increased DNA repair	Overexpression of DNA polymerase zeta	Eukaryocyte[71]
	Increased apoptosis inhibitors	High Bcl-2 protein family expression	Ovarian cancer cell line A2780[72]; drug-resistance cancer cell line[54]
Carboplatin	Increased efflux	Increased ATP7A, ATP7B mediated drug transport	Ovarian cancer cell line 2008[73]
	Increased detoxification	Upregulation of γ-glutamyltransferase and Glutathione	Cervical cancer cell line Hela[57]
	DNA	Genetic changes	Ovarian cancer cell line [58]
	Altered signal pathways	Activated Notch3, leading to cancer recurrence	Ovarian cancer cell line OVCAR3[59]
Oxaliplatin	Decreased drug uptake	Increased Ctr1 protein reduces the intracellular accumulation of oxaliplatin	Mouse embryo fibroblast[74]
	Increased DNA repair	Altered ERCC1, XPA protein expression	Colorectal cancer cell lines HT-29, HCT-8, SW620, HCT-116, COLO205, and Lovo[75]
	Transcription factor	Elevated levels of NFIB	Colorectal cancer cell line DLD1[62]
	Altered signal pathways	P53 high expression Activated Akt pathway by sCLU	Colorectal cancer cell line HCT116[33]; Hepatocelluar carcinoma[65]
	Increased apoptosis inhibitors	Increased PUMA expression	Colorectal cancer cell lines Lovo and SW116[63]
	Altered molecular chaperone	Increased Hsp90 protein expression	Colorectal cancer cell lines HCT116, SW620 and HT29; nude mice[64]

能会引起基因频繁突变、癌症相关蛋白启动子的甲基化等[60]。奥沙利铂体内耐药区别顺铂、卡铂的是错配修复系统的突变不同或者增强了旁路复制机制, 与NER(nucleotide excision repair)通路有关, 其中ERCC1(excision repair cross-complementation group 1)、XRCC1(X-ray cross-complementing group 1)、XDP(xeroderma pigmentosum group D)在奥沙利铂处理后呈一定的相关性, 可作为预测药物敏感性的指标[61]。除此以外, 在研究奥沙利铂耐药的结肠癌、膀胱癌细胞株中, 使用基因芯片技术, 发现180个基因普遍上调, 其中转录因子(14.6%)、代谢相关因子(14.6%)、转运相关蛋白(9.5%)、NFIB(nuclear factor I/B)都出现高表达, 而在顺铂耐药细胞中没有此现象[62]。具体来看, 奥沙利铂作用于结肠癌细胞HCT116后, 细胞周期被阻断在G_2-M期, 诱导凋亡。通过免疫荧光染色发现, 奥沙利铂诱导凋亡过程中, Bax蛋白移动至线粒体, 细胞色素C释放至细胞质, 后续实验发现抑制Bax或者p53使得HCT116细胞对奥沙利铂产生耐药[33]。PUMA(p53 up-regulate modulator of apoptosis)存在于内质网信号通路中, 在结肠癌细胞中发现与奥沙利铂耐药相关[63]。Moser等[64]研究发现, 抑制Hsp90(heat shock protein 90)可

以抑制癌细胞增殖和分化, 对结肠癌细胞的体外实验证实, 抑制Hsp90可以改善p53介导的奥沙利铂耐药, Hsp90可作为有效抑制结肠癌细胞增殖的靶标, 达到增敏奥沙利铂的效果。分泌丛生蛋白(secretory clusterin, sCLU)在多种类型的癌症细胞中表达并且与耐药有很大关系。对肝癌细胞的研究发现, sCLU过表达使得奥沙利铂引起的癌细胞凋亡减少, sCLU降表达后, 奥沙利铂抑制癌细胞生长, 并引起细胞凋亡增加, 通过后续实验发现sCLU通过激活Akt通路引起细胞对奥沙利铂的耐药[65]。

5 展望

总之, 铂类抗癌药物在治疗各种类型癌症中效果显著, 在治疗中结合一些其他药物可避免或者减少其副作用, 达到拓宽治疗领域的目的。目前, 已有第四代铂类抗癌药物赛特铂(satraplatin)在临床III期试验中, 这是第一个可口服的铂类抗癌药物, 与顺铂没有交叉耐药, 特别是在治疗前列腺癌(顺铂耐药)中效果显著。毒性与卡铂类似, 尚未发现严重的肾毒性、神经毒性、耳毒性[80-81]。最近几年随着对铂类药物在细胞内作用机理的深入研究, 有关铂类药物如何诱导DNA损伤、启动信号的传导、阻断细胞周期、激活或者抑制DNA修复以及诱导凋亡得到进一步了解。这些结果给我们提供了新思路: 一方面寻找一些药物佐剂, 以激活或者抑制相关信号通路, 达到增敏肿瘤细胞改善临床效果的目的; 另一方面通过分子生物学手段去发现与铂类药物作用机理相关的新蛋白或者信号通路从而为研发新的铂类抗癌药物提供理论基础。

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