顺铂联合用药治疗乳腺癌的研究进展

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摘要：乳腺癌发病率持续上升，严重影响女性健康。其治疗手段从手术治疗到化、放疗，再到内分泌治疗与免疫治疗，不断更新，但化疗仍是晚期乳腺癌或发生乳腺外转移的主要临床治疗手段。顺铂是治疗乳腺癌的一线化疗药物，但其不良反应和耐药性限制了其临床应用。目前众多研究报道顺铂联合其他药物可减轻顺铂不良反应、克服其耐药性，从而提高抗乳腺癌效果。本文拟对顺铂与天然活性成分、化疗药、抗体以及核酸类药联合治疗乳腺癌的最新研究进展进行综述，以期为乳腺癌联合治疗方案的选择提供参考。

关键词：顺铂；乳腺癌；联合用药；作用机制

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Research Progress of Cisplatin-based Combined Therapy in the Treatment of Breast Cancer

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ABSTRACT: The incidence of breast cancer continues to rise, which seriously affecting women's health. Its treatment methods including surgical treatment, chemotherapy, radiotherapy, and then endocrine therapy and immunotherapy, which are constantly updating. Chemotherapy is still the main clinical treatment strategy for advanced breast cancer or extramammary metastases. Cisplatin is a first-line chemotherapeutic drug for the treatment of breast cancer, but its adverse reactions and drug resistance limit its clinical application. At present, many studies have reported that cisplatin combined with other drugs can reduce the adverse reactions of cisplatin, overcome its drug resistance, so as to improve the anti-breast cancer effect. This article reviews the latest research progress of cisplatin combined with natural active ingredient, chemotherapeutic drugs, antibody and nucleic acid drugs in the treatment of breast cancer to provide some ideals for the selection of combined treatment for breast cancer.

KEYWORDS: cisplatin; breast cancer; combined medication; mechanism

乳腺癌的发病率占全身恶性肿瘤的 7%~10%，近年来呈年轻化趋势，严重危害女性健康[1]。乳腺癌的治疗手段从手术治疗到化疗、放疗，再到内分泌治疗与免疫治疗，不断更新，但化疗仍是晚期乳腺癌或发生乳腺外转移的临床主要治疗手段。顺铂是临床一线化疗药物，可治疗乳腺癌、肺癌等癌症[2-3]。顺铂通过阻止 DNA 双链解开和分离，抑制细胞分裂并诱导肿瘤细胞凋亡[4]，同时还可诱导线粒体内活性氧(reactive oxygen species，ROS)聚积，激活线粒体依赖性凋亡通路诱导细胞凋亡[5]。然而顺铂明显的肾、耳毒性以及耐药性致使其临床应用受限[6]。因此，临床上常采用顺铂与其他药物联用治疗乳腺癌，从而降低顺铂耐药性或减轻不良反应，提高其临床疗效。本文对近 10 年来顺铂与其他药物联合治疗乳腺癌的研究进展进行了概述，以期为乳腺癌的联合治疗提供参考。

1　顺铂联合天然活性成分

近年来，由于天然活性成分能显著抑制乳腺癌复发转移、逆转耐药以及调节机体免疫功能，降低顺铂毒性，改善患者生活质量，延长生存期，在乳腺癌治疗中的应用日益增多[7-8]。

1.1　黄酮类

天然黄酮类化合物具有抗肿瘤、抗炎、抗氧化等多种药理活性，是肿瘤预防或临床多药联合治疗方案的理想药物。黄酮联合顺铂通过多种作用机制来提高顺铂抗乳腺癌效果[9]。槲皮素是一种天然的小分子黄酮化合物，具有多种药理作用，不仅通过调控 PI3K/Akt、MAPK、Wnt/β-catenin 等信号通路抑制肿瘤细胞增殖、侵袭及转移、促肿瘤细胞凋亡等[10]；还可通过抑制 EGFR 磷酸化

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激活凋亡、有效抑制肿瘤生长，缓解顺铂对荷瘤鼠的不良反应，增强顺铂抗肿瘤作用[11]；同时它还抑制细胞色素 P4501B1 酶、CYP1B1 酶和 CYP1A1 酶的代谢，逆转三阴性乳腺癌(triple negative breast cancer，TNBC)细胞 MDA-MB-468 顺铂耐药[12]。木犀草素能阻滞乳腺癌细胞 MCF-7 周期于 G2/M 期和 S 期，抑制 TNF-α 诱导的 NF-κB 活性而降低顺铂耐药，进而发挥协同抗乳腺癌作用[13-14]。黄芩素既可增加顺铂对乳腺癌细胞 MCF-7 增殖抑制和促细胞凋亡，又可抑制乳腺癌细胞的转移[15]。槲皮素可通过抑制 EGFR 磷酸化激活凋亡、有效抑制肿瘤生长，缓解顺铂对荷瘤鼠的毒副作用，增强顺铂抗肿瘤作用；同时槲皮素还可抑制细胞色素 P4501B1 酶、CYP1B1 酶和 CYP1A1 酶抑制代谢，逆转三阴性乳腺癌细胞 MDA-MB-468 顺铂耐药[16]。另有研究表明黄芪总黄酮可通过 IL- 6/STAT3 通路，有效上调免疫因子 IL-2、IFN-γ、$CD3^+$、$CD4^+$、$CD4^+/CD8^+$水平，下调 IL-1、IL-6、TNF-α、$CD8^+$水平，减轻顺铂免疫抑制作用，增强顺铂治疗乳腺癌疗效[17-18]。但目前黄酮化合物联合顺铂用于临床乳腺癌患者治疗较少，这可能与大多数黄酮类化合物生物利用度不高有关。

1.2 生物碱类

多种天然生物碱类成分不仅具有抗肿瘤、抗菌等生物活性，且能减轻化疗药物的不良反应和提高机体免疫功能等[19]。如紫杉醇是从红豆杉属植物中提取的一种二萜类生物碱，可破坏微管和微管蛋白二聚体之间的动态平衡，加速微管聚集，装配稳定的微管，导致细胞周期停滞 G2/M 期和 S 期，抑制肿瘤细胞增殖[20]，它联合顺铂可诱导乳腺癌细胞凋亡，明显改善患者 EGFR、HER-2 受体阳性表达状态，但伴随骨髓抑制、神经毒性、呕吐等可耐受的不良反应，具有一定的临床推广价值[21-22]。长春瑞滨与顺铂联用无相互交叉耐药，能协同促肿瘤细胞凋亡[23-24]，蒋顺等[25]采用两药联合治疗 46 例晚期乳腺癌患者，总有效率高达 86.96%，明显高于单药长春瑞滨组(34.78%)，不良反应可耐受、安全性好。苦参碱激活 JNK1/AP-1 信号通路，调控 p53、Bax 等凋亡相关蛋白表达，促乳腺癌细胞凋亡；苦参碱与顺铂等化疗药联用治疗 37 例中、晚期乳腺癌患者有效率(55.6%)高于单化疗组(47.4%)[26-27]。粉防己碱可激活 caspase 通路和细胞内 ROS 介导的凋亡作用，且抑制 ATP7A 的高表达来逆转顺铂耐药，对 MDA-MB-231 细胞具有良好的协同细胞毒性作用[28-30]，但它没有像紫杉醇、长春瑞滨和苦参碱一样应用于临床乳腺癌患者，还需进一步的临床验证疗效与不良反应评价研究。

1.3 多酚类

多酚类化合物是有效的天然抗肿瘤防护与治疗剂，可以直接杀死肿瘤细胞，也可以通过抑制血管生成、诱导细胞周期阻滞、影响信号通路以及抑制细胞增殖和迁移等，与顺铂发挥协同抗乳腺癌作用[31]。白藜芦醇能增强顺铂对 MDA-MB-231细胞迁移和侵袭的抑制，其机制可能是与 PI3K/AKT、NF-κB、JNK、ERK 信号通路相关[32]；另外白藜芦醇还能提高 MCF-7 细胞对顺铂的敏感性[33]，但由于其生物利用度低，未与顺铂联合用于临床患者治疗。姜黄素是从姜黄等根茎中提取的酸性多酚，可通过下调 miR-7641 促进 PTPN14、FEN1 的表达，抑制 ERK 磷酸化，增强顺铂敏感性，降低顺铂对正常细胞的毒性，进而发挥协同抗乳腺癌功效[34-36]。去甲斑蝥素通过抑制 Wnt/β-catenin 信号通路，降低血管内皮生长因子(vascular endothelial growth factor，VEGF)与 DLL4 蛋白表达，减少管腔形成、抑制肿瘤新生血管生成，多途径抑制乳腺癌细胞增殖、迁移[37]。茶多酚通过抑制 NF-κB 和 VEGF 表达抑制血管生成，靶向 DNA 修复内切酶 ERCC1-XPF，激活 Nrf2-ARE 信号通路，诱导细胞周期阻滞和增强顺铂敏感性，增强机体免疫且减轻顺铂所致肾毒性[38]，且茶多酚与顺铂联用可稳定患者的白细胞计数，改善患者生活质量[39]，为乳腺癌患者临床治疗提供一种新思路。

1.4 萜类

萜类化合物具有较强的抗肿瘤活性[40]，与顺铂联用发挥协同抗乳腺癌作用[41]。如雷公藤甲素及其衍生物阻滞 TNBC 细胞周期 S 期；减弱 XRCC1、PARP1 和 RAD51 蛋白表达，影响 XRCC1/ PARP1 信号通路传导，增强 TNBC 细胞对顺铂的敏感性，促进雷公藤甲素在 TNBC 临床治疗中的应用[42]。榄香烯[43]和穿心莲内酯[44]均阻滞 MCF-7 细胞于 G0/G1 期，干扰 DNA 合成和蛋白质代谢，促进顺铂诱导凋亡，抑制顺铂诱导自噬，进而提高顺铂化疗效果。也有研究结果表明三萜皂苷黄芪甲苷通过调控 Bax/Bcl-2/caspase-3 凋亡信号通路，上调免疫

因子 IL-2、IFN-γ、$CD3^+$、$CD4^+$等水平及下调 IL-1、IL-6、TNF、$CD8^+$水平，协同抑制乳腺癌细胞增殖、迁移和诱导凋亡[45]。萜类化合物与顺铂联合治疗乳腺癌目前主要集中于体外细胞水平研究，体内研究以及应用乳腺癌患者治疗的研究极少。

1.5 其他类

其他天然活性成分如多糖等也与顺铂联合用于抗乳腺癌研究[46]。乌贼墨多糖联合顺铂下调 MDA-MB-231 细胞中 MMP-2、MMP-9 表达，从而阻断 PI3K/AKT/mTOR 通路，抑制肿瘤细胞生长；同时调节 Bcl-2/Bax 基因比例和 caspase 酶表达，显著降低肿瘤细胞自噬相关蛋白 LC3-II、beclin-1 及 P13K-Akt、p38 MAPK信号通路中的关键调控因子 p-Akt 和 p-p38 的表达，拮抗自噬，从而杀死肿瘤细胞[47-48]。其他天然活性成分与顺铂联合抗乳腺癌研究见表 1[49-53]。

2 顺铂联合中药复方制剂

中药复方制剂既能抗肿瘤，还益气补血，提高机体免疫力，尤其对因长期化疗而正气虚弱的晚期肿瘤患者有较好的疗效[54]，与顺铂发挥抗乳腺癌效果。参芪扶正注射液可下调耐顺铂 MDA-MB-231 细胞中 P-糖蛋白表达，提高顺铂敏感性，降低顺铂诱导的 IL-10 和 PGE2 释放，改善免疫，从而发挥良好的协同抗乳腺癌效应[55]。逍遥篓贝散促进淋巴母细胞转化，抑制肿瘤生长，促进细胞免疫和体液免疫，与顺铂联用协同增加抑瘤作用的同时，还一定程度上减轻顺铂的不良反应[56]。抑木扶土法(柴芍夏朴汤)联合 GP(吉西他滨+顺铂)方案治疗晚期乳腺癌，改善晚期乳腺癌患者临床症状，提高其生活质量，减轻化疗不良反应[57]。中药复方制剂与顺铂联用在一定程度上避免了单一化合物治疗局限，提高顺铂敏感性，减轻顺铂不良反应，能多方位、多靶点作用乳腺癌，进而提高抗肿瘤作用。但复方制剂中具体有效的中药成分尚不十分明确，相关机制存在多样性，应用临床患者可能还有一些未知不良反应，故需更多严谨试验确证中药复方联合顺铂治疗乳腺癌的疗效。

3 顺铂联合化疗药物

顺铂联合其他化疗药应用乳腺癌治疗的研究较多，既有细胞水平研究报道，也有应用临床患者的研究，其研究结果主要表现为协同增效、降低或逆转顺铂耐药。如吉西他滨联合顺铂激活 mTOR/S6K1/NF-κB 信号通路，上调 NF-κB 蛋白和 mRNA 表达，下调 mTOR、S6K1 蛋白，改变能量代谢，抑制细胞增殖，促进乳腺癌细胞裂解死亡[58]。李伟等[59]报道吉西他滨与顺铂联合治疗 120 例晚期乳腺癌患者，结果表明其对 TNBC 疗效优于非 TNBC 组，且 TNBC 组和非 TNBC 组的客观缓解率分别为 38.5%和 22.1%，疾病控制率分别为 75.0%和 57.4%，mPFS 分别为(8.2±2.7)个月和(5.9±1.5)个月。多西他赛与顺铂联合治疗术后出现胸壁局部复发和区域淋巴结转移的 TNBC 患者疗效较好，且 Ki-67 阳性表达的 TNBC 患者对多西他赛联合顺铂化疗方案更敏感[60]。另有研究证实对蒽环类耐药的晚期乳腺癌患者使用顺铂和多西他赛注射液联合治疗显著延长患者生存期[61]。顺铂与其他化疗药物联合抗乳腺癌作用见表 2[62-74]。

4 顺铂联合单抗

曲妥珠单抗是以 HER 受体家族为靶点的药物，能阻断 HER2/neu 介导的 PI3K 及 MAPK 信号通路，减少 VEGF 产生，抑制肿瘤血管生成，用于治疗 HER2 阳性乳腺癌[75]。该单抗药物与顺铂联用可增强顺铂对乳腺癌细胞抑制作用[76-77]，明显减少顺铂引起的非常规 DNA 合成[78]，能够显著提高 HER2 过度表达的转移性乳腺癌疗效。贝伐珠抗体可特异结合 VEGF，抑制其刺激细胞膜上的 VEGF 受体、阻断肿瘤血管生成，抑制肿瘤生长，增强顺铂的化疗效果[79]，且临床研究表明贝伐单抗联合 TP 方案治疗晚期乳腺癌疗效显著，有效改

表 1 天然活性成分与顺铂联合治疗乳腺癌

Tab. 1 Combination of natural active ingredients and cisplatin in the treatment of breast cancer

化合物	类别	研究阶段	抗乳腺癌机制及功效	文献
天南星多糖	多糖	临床前(体外)	抑制 PI3K/Akt 通路激活，抑制 MDA-MB-231 细胞增殖、凋亡及上皮间质转化，提高顺铂敏感性，降低肿瘤标志物水平	[49]
槐耳多糖	多糖	临床前(体外)	激活 mTOR 信号提高顺铂敏感性，通过 PI3K/AKT 信号通路降低氧化应激和促细胞凋亡，降低顺铂肾毒性	[50-51]
芦荟大黄素	蒽醌	临床前(体外)	阻滞 MDA-MB-231 细胞周期 G1 期，激活凋亡酶 caspase-3 且抑制端粒酶诱导细胞凋亡，发挥协同增敏作用	[52]
维生素 C	维生素	临床前(体外)	促进 caspase-3 表达和抑制 Bcl-2 表达来协同抑制 MCF-7 细胞增殖、诱导细胞凋亡	[53]

表 2 其他化疗药物与顺铂联合治疗乳腺癌

Tab. 2 Other chemotherapy drugs combined with cisplatin in the treatment of breast cancer

药物名称	研究现状	抗乳腺癌机制及功效	参考文献
阿霉素	临床前	激活 NF-κB 信号通路，调控 P53 表达，诱导乳腺癌细胞凋亡	[62-63]
氟尿嘧啶	临床前、临床(25 例)	调控 P53 表达，诱导乳腺癌细胞凋亡；对转移性乳腺癌患者联合治疗有效且安全，部分缓解率为 32%，疾病控制率为 68%，中位进展时间及生存期分别为 5 和 6 个月	[64-65]
依托泊苷	临床前	作用 DNA 拓扑异构酶进而抑制 DNA 合成，阻滞细胞周期晚 S 期或早 G2 期	[66]
比卡鲁胺	临床前	通过调控 PKC-EMT 过程抑制 MDA-MB-453 及 BT-549 细胞增殖，显著诱导乳腺癌细胞凋亡	[67]
培美曲塞	临床(45 例)	总疾病控制率达 67.7%，总部分缓解率、无进展生存期及总生存期效果满意，不良反应患者多能够耐受，严重不良反应以骨髓抑制为主	[68]
阿帕替尼	临床前、临床(46 例)	抑制肿瘤血管生成，还可通过 VEGFR2-Akt-mTOR 信号通路增强顺铂抗乳腺癌，可显著提高晚期三阴性乳腺癌患者的客观缓解率及疾病控制率	[69-70]
西达苯胺	临床前	降低 ERCC1 表达，抑制停滞在 G2/M 期的损伤 DNA 修复，尤其减少对顺铂诱导的 DNA 络合物的清除，减少顺铂耐药性	[71]
来那度胺	临床前	抑制 VEGF、bFGF，抑制肿瘤细胞血管生成，且诱导 caspase-3 和裂解 PARP 表达而降低 Bcl-2 的表达，协同顺铂诱导乳腺癌细胞凋亡	[72]
索拉菲尼	临床前	协同抑制 ERK 的磷酸化，抑制 ERK 通路的活性，从而抑制肿瘤细胞的增殖	[73]
替吉奥	临床(160 例)	用于肝脏转移乳腺癌患者治疗效果较好，但抗乳腺癌效果不如洛铂联用替吉奥	[74]

善相关细胞因子(VEGF、IL-4、IL-10、TNF-α)水平，安全可靠，值得临床推广[80]。尼妥珠单抗是中国第 1 个用于治疗恶性肿瘤的功能性单抗药物，与 EGFR 特异结合，竞争性抑制其与配体结合，阻断 EGFR 介导的信号传导和细胞学效应，降低 BRCA1 蛋白表达，使细胞 MDA-MB-231 不能修复顺铂引起的 DNA 损伤而提高对顺铂敏感性[81]。

5 顺铂联合核酸药物

耐药是顺铂临床应用受限的主要原因之一。国内外研究发现 microRNA(miRNA)、小干扰 RNA(siRNA)等核酸药物能降低或逆转顺铂耐药，从而提高顺铂抗乳腺癌作用。miRNA 是一种细胞内源性的非编码单链 RNA，能通过调控肿瘤相关基因来实现对肿瘤增殖抑制和促进凋亡的作用[82]。研究发现 miR-221/222[83-85]、miR-106b[86]、miR-342-3p[87]、miR-182[88]等均可调控细胞凋亡相关基因表达，诱导细胞凋亡，增强乳腺癌细胞对顺铂化疗敏感性。siRNA 可以诱导基因沉默，也广泛应用于乳腺癌等肿瘤治疗[89]。有研究证实趋化因子受体 4 能增加乳腺癌细胞对顺铂敏感性[90]。有关顺铂联合核酸药物治疗乳腺癌研究目前主要集中在降低或逆转顺铂耐药方面，其他研究相对较少且多数研究仅停留在细胞水平。

6 顺铂联合其他类药物

顺铂除联合上述药物治疗乳腺癌外，也与其他类药物联合用于抗乳腺癌研究。如氨磷汀在碱性磷酸酶影响下水解为巯基化合物 WR-1605，而 WR-1605 的自由巯基能够在细胞内直接与顺铂结合，清除放、化疗中产生的氧自由基，阻抑过氧化物对细胞的伤害，保护正常细胞，减轻顺铂不良反应[91]。有研究者分别采用氨磷汀联合吉西他滨与顺铂用于 52 例晚期乳腺癌患者治疗，吉西他滨与顺铂为对照组，研究发现联合治疗组、对照组的有效率及疾病控制率基本相当，但联合治疗组骨髓抑制及周围神经毒性发生率明显降低。另有其他药物联合顺铂治疗乳腺癌的研究见表 3[92-95]。

7 展望

目前顺铂与多数天然活性成分、中药复方制剂、化疗药等联合治疗乳腺癌，其疗效显著优于顺铂单药处理组，减少了顺铂不良反应，降低或逆转顺铂耐药，且部分联合用药策略延长乳腺癌患者生存期，提高患者的生活质量。虽然顺铂与

表 3 其他药物与顺铂联合治疗乳腺癌

Tab. 3 Other drugs combination with cisplatin in the treatment of breast cancer

药物名称	研究现状	抗乳腺癌机制及功效	参考文献
甲基乙二醛	临床前	通过 ATP 消耗影响糖酵解和线粒体呼吸来使乳腺癌细胞对顺铂敏感，协同诱导程序性细胞死亡和抑制干细胞	[92]
双硫仑	临床前	抑制 ALDH 活性和干细胞相关转录因子 Sox、Nanog、OCT 的表达，调节细胞内 ROS 的产生，逆转顺铂对 ALDH 细胞的耐药性	[93]
来曲唑与紫杉醇	临床(92 例)	抑制 ER-MAPK-Elk-1 途径，下调 FEN1 的表达增强顺铂敏感性。来曲唑与紫杉醇联合顺铂的总有效率高于对照组来曲唑与紫杉醇(63.04%)，达 89.13%，且转移性乳腺癌患者治疗后的认知功能、情绪功能、角色功能、生活总质量等显示更好	[94-95]

上述有些药物联用的试验结果令人鼓舞，但仍有许多问题有待解决。首先，已开展的顺铂联合用药研究多数仅停留临床前研究，联用的长期疗效和安全性尚未深入研究。其次，有些应用于临床乳腺癌患者联合治疗研究纳入的样本量小，研究结果还不能完全反映临床的真实情况。此外，顺铂与中药复方制剂联用在抗乳腺癌方面可能产生协同或相加作用，但其具体机制大多尚未明确，有待进一步研究。

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