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评 述 中医药与重大疾病防治专辑

中药抗肿瘤的增效减毒效应研究进展

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摘要 化疗、靶向治疗和免疫治疗是恶性肿瘤药物治疗的主要手段, 然而, 毒副作用和耐药性是限制抗肿瘤药物疗效的关键原因. 中药是补充与替代医学的重要组成部分, 不仅能预防肿瘤的发生发展, 提高西药抗肿瘤的疗效, 还能缓解西药抗肿瘤产生的毒副反应, 提高患者生存质量. 本文围绕中药对化疗药、靶向药和免疫检查点抑制剂的增敏增效、逆转耐药、增强机体免疫应答的作用, 以及减轻对正常组织器官的毒副作用等方面阐述中西医结合抗肿瘤的研究进展, 提出了抗肿瘤西药减毒增效的新途径. 然而, 中药在防治恶性肿瘤等重大疾病的临床应用中也存在很多问题, 如成分复杂, 缺乏严格的质量控制; 缺乏大样本、高质量的临床试验疗效证据支持; 药效物质基础及机制研究不足等. 本文最后对中西医结合抗肿瘤的研究方向进行了展望, 以期揭示中药防治重大疾病的科学内涵, 传承和发展中医药理论.

关键词 中药, 中西医结合, 肿瘤, 增效, 减毒

癌症作为全球第二大死亡因素, 死亡例数和发病例数逐年上升. 世界卫生组织国际癌症研究机构(International Agency for Research on Cancer, IARC)发布的数据显示, 2020年全球新发癌症病例1929万例, 其中中国新发癌症457万人, 占全球23.7%; 癌症死亡病例996万例, 其中中国癌症死亡人数300万, 占癌症死亡总人数的30%[1]. 由于中国是世界第一人口大国, 癌症新发人数和死亡人数远超世界其他国家. 随着社会老龄化加剧, 预计2040年全球癌症新发病例将达到2840万例, 比2020年增长47%[1]. 因此, 未来全球癌症预防和治疗仍将面临巨大挑战.

目前, 对于恶性肿瘤的常规治疗手段主要有外科手术、化疗、放疗、靶向治疗和免疫治疗等. 其中, 药物治疗在肿瘤的综合治疗中占有重要地位. 然而, 毒副作用和耐药是限制肿瘤一线药物疗效的主要原因[2]. 中医药作为补充与替代医学的重要组成部分, 经过数千年的发展, 形成了自己独特的理论体系和诊疗体系. 研究表明, 中医药作为西医治疗的辅助手段, 在癌症的预防和治疗中发挥了重要作用, 不仅能够预防肿瘤发生, 使肿瘤缩小或稳定, 减少肿瘤复发和转移,

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还能保护患者免受并发症的困扰, 增加机体对常规治疗的敏感性, 减少副作用, 提高患者生活质量, 延长生存期[3,4]. 中西药联用, 中西医优势互补, 是我国肿瘤治疗领域的特色. 然而, 中药在抗肿瘤治疗中发挥的作用有许多未知之处, 值得深入探索. 本文阐述了西药抗肿瘤的治疗现状及目前存在的问题, 总结了中药在抗肿瘤治疗中的减毒增效作用及机制, 讨论了中药抗肿瘤目前存在的问题和可能的解决方案.

1　西药抗肿瘤的治疗现状及目前存在的问题

1.1　癌症全球现状

手术、放化疗法、靶向疗法和免疫疗法是目前用于控制肿瘤生长, 延长患者存活时间的主要手段, 在一定程度上降低了癌症患者的死亡率, 提高了生活质量. 2020年全球发病率前十的癌症分别为乳腺癌、肺癌、结直肠癌、前列腺癌、胃癌、肝癌、宫颈癌、食管癌、甲状腺癌和膀胱癌, 这十种癌症占据新发癌症总数的63%, 其中肺癌死亡率居全球第一[1]. 自1991年以来, 癌症死亡率持续下降, 至2018年总体下降了31%[5]. 与此同时, 生存率不断提升, 2010~2016年期间被诊断出的所有癌症5年相对生存率上升为67%, 其中, 前列腺癌的生存率最高(98%), 其次为黑色素瘤(92%)和乳腺癌(90%), 生存率最低的是胰腺癌(9%)、其次为肝癌(18%)、肺癌(19%)和食管癌(20%)[6]. 癌症总体死亡率下降得益于吸烟者减少(致肺癌死亡率大幅下降)、医疗水平提高以及癌症早筛的普及, 但一些癌种如乳腺癌、前列腺癌和结直肠癌, 临床治疗进展正在放缓或停止.

1.2　西药抗肿瘤目前存在的问题

常规抗肿瘤疗法单独或联合使用具有许多局限性: (ⅰ) 化疗和放疗是中晚期恶性肿瘤患者的首选疗法或主要术后辅助疗法, 但存在诸多副作用和并发症, 如化疗性周围神经毒性、骨髓抑制、胃肠道反应、肝肾功能损伤或局部辐射损伤等; 此外, 长时间放化疗会使肿瘤细胞产生耐药性, 导致其对现有放化疗法不再敏感. (ⅱ) 靶向治疗作为一种新型的抗肿瘤疗法, 对于已经明确的致癌靶点, 可以更精确高效地识别和攻击肿瘤细胞. 然而, 一些药物靶点也存在于正常细胞中, 易引起皮肤毒性、心血管毒性、胃肠道毒性等毒副作用, 且长时间应用容易产生耐药性[7]; 此外, 靶向药物价格较高, 多数患者负担不起. (ⅲ) 免疫疗法, 包括免疫检查点抑制剂、癌症疫苗和T细胞疗法等, 是另一类新型抗肿瘤方法, 通过刺激免疫细胞以增强其抗癌活性; 然而, 免疫治疗在提高患者生活质量和延长生存时间方面的优势目前尚不确切, 也会引发一系列毒性反应包括皮肤毒性、消化系统毒性、甲状腺毒性等[8~11]; 此外, 免疫疗法价格昂贵, 绝大多数患者负担不起. 因此, 开发更有效或对现有疗法具有减毒增效作用的抗肿瘤疗法是目前临床上的迫切需求.

2　中药对西药抗肿瘤的增效作用

2.1　中药增强化疗药的抗肿瘤疗效

临床上使用的化疗药种类繁多, 主要包括烷化剂、有丝分裂抑制剂、拓扑异构酶抑制剂、抗肿瘤抗生素和抗代谢类药物等. 化疗药通过诱导肿瘤细胞坏死或程序性死亡(如细胞凋亡或自噬)发挥抗肿瘤作用. 尽管是最常用的抗癌药物, 化疗的预后和疗效却仍不尽如人意. 除了严重的副作用外, 癌细胞产生内在或获得性耐药是临床上影响化疗药抗肿瘤疗效的主要障碍[12,13]. 化疗药产生耐药的机制有多种, 主要包括药物代谢的变化、药物外排泵的过度表达、DNA修复的变化、肿瘤干细胞的形成、免疫抑制、凋亡基因失活和抗凋亡基因激活, 以及肿瘤细胞代谢重编程等[14~16]. 参与化疗耐药的蛋白或信号通路主要有NF-κB/HIF-1α/ROS, PI3K/AKT, p53, Bcl-2/Bax/Caspase-3, MDR1, P-gp等[17].

中医药作为一种补充和替代疗法越来越被接受[18]. 很多研究表明, 中药与常规化疗药联合应用可通过多种分子机制增强化疗药的抗肿瘤疗效. 异呋喃二烯是一种植物来源的生物活性倍半萜烯, 具有广泛的抗肿瘤特性. 近期研究表明, 异呋喃二烯通过引起ROS-依赖的DNA损伤与替莫唑胺发挥协同抗胶质瘤作用[19]. Pan等人[20]发现, 小檗碱在体内外均可通过调控AMPK/HIF-1α/P-gp信号通路逆转乳腺癌细胞对多柔比星的化疗耐受性, 并直接诱导细胞凋亡. 葫芦素E是一种广泛分布于中草药中的天然三萜, 具有抗肿瘤作用. 葫芦素E可通过调控TFAP4/Wnt/β-catenin信号通路降低ATP依赖性跨膜转运蛋白ABCC1和MDR1的

表达来提高大肠癌细胞对化疗的敏感性，证明葫芦素E可作为大肠癌治疗的增敏剂[21]. 肠道微生物可通过改变药物代谢能力和宿主代谢稳态影响化疗药的抗肿瘤疗效. 研究发现, 灵芝孢子中提取的多糖通过重塑肠道菌群抑制肿瘤细胞代谢，增强乳腺癌对紫杉醇的敏感性, 并可恢复紫杉醇引发的肠道菌群失调[22].

在我国，临床医生根据辨证施治原则常采用不同的中药方剂与化疗药相结合，以达到肿瘤治疗减毒增效的目的. 一项对参芪扶正注射液治疗晚期胃癌的系统荟萃分析发现，与单独采用化疗方法相比，化疗联合参芪扶正注射液可提高患者的完全缓解(优势比OR=1.68)和部分缓解有效率(OR=1.32), 并显著改善患者生活质量，减少恶心、呕吐、口腔黏膜炎、白细胞减少等不良反应的发生(OR=3.05)[23]. 此外，与单独使用铂类化疗药相比，参芪扶正注射液与铂类化疗药联合治疗晚期非小细胞肺癌(non-small-cell lung cancer, NSCLC)和结直肠癌使肿瘤治疗响应率提高19%, 并能显著降低多种不良反应发生率[24,25]. 从中药薏苡仁中提取的有效成分康莱特注射液联合化疗药治疗晚期NSCLC的临床试验表明，与单独使用化疗药相比，联合用药可显著提高患者的客观响应率(RR=1.35), 提高患者生存质量(RR=2.04)，并降低胃肠道副反应风险(RR=0.53)[26~28]. 华蟾素注射液联合铂类、吉西他滨等化疗药治疗NSCLC、胃癌、胆囊癌等可显著提高患者的客观响应率(RR=1.18~1.43)，提高1年期和2年期生存率(RR分别为1.12和1.72)，改善患者的生活质量(RR=1.62)[29~31]. 鸦胆子油乳剂注射液与化疗药联用治疗NSCLC可使患者客观响应率提高25%，并显著提高患者生存质量(RR=1.87)，降低恶心呕吐等副反应(RR=0.67)[32,33]. 这些研究表明，中药可作为化疗药的增敏剂起到协同抗肿瘤作用.

2.2 中药增强免疫检查点抑制剂的抗肿瘤疗效

近年来, 肿瘤免疫疗法取得了重大进展, 主要包括免疫检查点抑制剂、CART细胞疗法和肿瘤疫苗等. PD-1/PD-L1是目前已知的重要免疫检查点之一，其单克隆抗体通过阻断PD-1与PD-L相互作用可重新激活T细胞, 从而操纵免疫系统攻击癌细胞, 用于多种实体瘤的治疗[34]. 然而，单独使用免疫检查点抑制剂PD-1/PD-L1抗体治疗非小细胞肺癌、皮肤黑色素瘤、头颈癌等的反应率仅有15%~40%，同时，多数患者初步反应后出现肿瘤复发，产生获得性耐药[35]. 临床上主要采用PD-1/PD-L1抗体联合化疗药或CTLA-4抗体等治疗肿瘤，虽然可提高肿瘤控制率，但副作用也相对增加[36~38].

中药在调节机体免疫功能方面具有重要作用，从中药中发现免疫增敏剂，对于延缓肿瘤耐药、减轻副作用具有重要的临床意义. 研究发现，清热解毒中药鸦胆子的主要活性成分鸦胆子苦醇可显著增强黑色素瘤对PD-1抗体的敏感性, 提高$CD8^+$和$CD4^+$ T细胞诱导的肿瘤细胞浸润, 抑制Treg细胞, 促进T细胞激活[39]. 鸦胆子苦醇是Nrf2的靶向抑制剂, 此研究还发现, PD-L1的表达受Nrf2直接调控[39,40]. 因此，靶向抑制Nrf2和PD-1抗体联合治疗为克服肿瘤的免疫耐受提供了重要替代策略.

“扶正固本”是中医治疗癌症的重要法则. 肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)在肿瘤发展及转移等阶段中起关键作用, 促使TAM向M1型巨噬细胞极化将会抑制肿瘤的发展及转移[41]. 研究发现, 补气中药人参来源的纳米颗粒(ginseng derived nanoparticles, GDNPs)对单核-巨噬细胞有很强的亲嗜性, 能诱导TAM向具有抗肿瘤作用的M1型巨噬细胞极化, 分泌大量ROS杀伤肿瘤[42]. GDNPs还可通过活化巨噬细胞表面的TLR4, 解除肿瘤微环境免疫抑制状态, 活化$CD8^+$ T细胞和NK细胞, 从而抑制肿瘤的生长. 进一步研究表明, GDNPs可以重编程TAM, 增加CCL5和CXCL9分泌, 招募$CD8^+$ T细胞进入肿瘤床, 与PD-1抗体联用具有协同抗肿瘤疗效，且无明显副作用[43~45]. 中药来源的天然囊泡与免疫检查点抑制剂联用增强抗肿瘤效果为肿瘤治疗提供了新策略.

肠道微生物直接或间接参与恶性肿瘤的发生和发展. 中药复方含有多种益生元成分, 可改变肠道微生物的组成, 调节菌群平衡. 研究表明, 肠道微生物可能在肿瘤微环境水平上影响PD-1抗体的疗效[46]. 多数结直肠癌是微卫星稳定型，对免疫检查点抑制剂没有反应[47]. 葛根芩连汤是治疗溃疡性结肠炎的经典方剂. 研究表明，葛根芩连汤与PD-1抗体联用可通过改变肠道菌群组成有效抑制异种移植模型中CT26肿瘤的生长, 增加$CD8^+$ T细胞的比例和IFN-γ的表达[48]. 脂质代谢失调, 如鞘磷脂酶2低表达导致的鞘磷脂催化能力降低有助于肿瘤细胞的免疫逃逸, 降低PD-1抗体疗效[49]. 葛根芩连汤还可通过调节鞘磷脂和甘油磷脂代谢途

径, 增强PD-1抗体对结直肠癌的作用. 中药方剂与免疫检查点抑制剂联用为微卫星稳定型肿瘤的治疗提供了新策略.

2.3　中药克服肿瘤耐药增强分子靶向药的抗肿瘤疗效

以分子靶向药为基础的精准医学在癌症的治疗中取得了显著进展, 但如何克服其产生的耐药是临床上公认的难题. 表皮生长因子受体酪氨酸激酶抑制剂(EGFR-TKIs)是目前应用最广、最具代表性的肺癌靶向药物, 有吉非替尼、阿法替尼、奥希替尼等, 能与EGFR特异性结合, 阻断肿瘤生长信号通路[50,51]. 虽然EGFR-TKIs对NSCLC具有较好的临床疗效, 但是大多数患者在使用EGFR-TKI, 如吉非替尼和厄洛替尼一年后会发生耐药, 机制包括: (ⅰ) EGFR突变, 包括T790M, C797S等[52]; (ⅱ) 旁路或下游信号通路异常激活, 包括MET/HER2扩增, AXL和CDCP1共激活, STAT3和YAP1过度激活等, 使EGFR-TKI脱靶[53~55]; (ⅲ) 组织学类型转变, 如上皮-间质转化或者NSCLC-小细胞肺癌转化等[56], 但是依然有近50%的EGFR-TKIs耐药机理尚不清楚. 因此, 寻找EGFR-TKI耐药的分子机制和克服耐药的方法是亟待解决的关键问题.

临床样本分析发现, STAT3的水平与EGFR突变的NSCLC患者无进展生存期呈负相关, 揭示了STAT3过度激活是NSCLC耐药的新机制[54]. 针对STAT3信号通路, 从中医常用治疗“肺积”和“息贲”的中药中发现, 栀子活性成分CS-Ⅳa-Be可靶向IL-6Rα阻断IL-6与IL-6Rα的相互作用, 进而抑制STAT3通路的活性[57]; 吴茱萸活性成分吴茱萸碱通过选择性上调酪氨酸磷酸酶SHP-1的表达, 抑制JAK2激酶的磷酸化, 从而抑制STAT3的活化[58]; 毛萼香茶菜活性成分毛萼乙素可共价结合于STAT3而抑制其磷酸化和激活[59]; 双氢青蒿素可通过抑制STAT3增加非小细胞肺癌细胞对吉非替尼的敏感性[60], 还能通过升高ROS水平破坏血红素代谢来逆转EGFR突变型NSCLC对奥希替尼的耐药[61]; 另有体内外研究表明, 黄连解毒汤能通过STAT3/Bcl-2信号通路增强厄洛替尼对EGFR突变的NSCLC细胞的敏感性[62]. 这些研究为克服EGFR-TKI的耐药提供了天然候选药物.

肺癌患者本身正气不足, 而靶向药多属于攻伐之毒, 易在体内热化, 伤津耗液, 致肺阴亏虚. 中医认为, 正气亏虚、余毒内蕴是导致EGFR-TKI获得性耐药的主要病机, 联合扶正祛邪、益气养阴中药可使EGFR-TKI增敏增效[63]. 临床上常用的中药方剂主要有消癌平注射液、参一胶囊、金复康口服液、扶正抗癌方等, 根据患者的身体状况进行辨证施治. 一项纳入354位EGFR突变阳性的晚期NSCLC患者随机、双盲临床试验[64]表明, EGFR-TKI与中药联用组的中位无进展生存期为13.50个月, 显著长于EGFR-TKI组(10.94个月, P=0.0064). EGFR-TKI与中药联用组患者总缓解率显著高于EGFR-TKI组(64.32% *vs*. 52.66%, P=0.026). 与中药联用还能提高患者生存质量, EGFR-TKI导致的药物相关不良事件(包括腹泻、瘙痒、皮疹、食欲不振和疲劳等)较少见. 一项回顾性研究也证实, 在使用一线EGFR-TKI治疗期间联合中药治疗, 无进展生存期和总生存率高于未联合中药治疗的患者组[65].

3　中药对西药抗肿瘤的减毒作用

化疗属于全身性治疗, 虽然应用普遍, 但对正常组织器官的毒副作用较大. 化疗药的毒副作用分为近期毒副作用和远期毒副作用两种. 近期毒副作用包括对神经系统、造血系统、肝肾功能、消化系统、免疫系统、皮肤和黏膜、心脏等的毒副作用; 远期毒副作用主要有生殖障碍、致癌、致畸作用等[66]. 与化疗药相比, 靶向药和免疫疗法能更精确高效地识别和攻击肿瘤细胞, 然而, 由于一些药物靶点也存在于健康细胞中, 所以也会引起一些毒副作用, 包括皮肤毒性、胃肠道毒性等. 中医认为, 肿瘤治疗过程中全身或局部机能状况失衡是导致毒副反应发生的主要原因. 通过辨证论治, 运用中药的偏性调整机体的偏盛偏衰从而调动内在的抗病能力, 减轻西药抗肿瘤的毒副作用而达到整体调控的效果[67].

3.1　中药降低化疗引起的外周神经毒性

奥沙利铂等化疗药引起的外周神经毒性(chemotherapy-induced peripheral neurotoxicity, CIPN)是肿瘤治疗最常见的毒副反应之一, 发生率高达70%~100%, 主要症状为麻木、本体感受丧失和痛觉超敏[68]. CIPN导致化疗剂量减少或化疗提前中止, 严重影响患者生存及预后. 目前临床上依然缺乏缓解CIPN的有效药物, 如何防治CIPN是癌症治疗急需解决的共

识难题. 中医学认为, CIPN归属于“血痹”“痹证”等范畴, 气阴两虚、血脉瘀阻是CIPN的主要病理基础[69~71], 临床上常以通阳行痹、益气养阴、温经散寒为治疗原则, 主要治疗方法有中药内服、中药外治和针灸等[72]. 临床疗效较好的中药方剂主要有黄芪桂枝五物汤、温经和血通痹方和补阳还五汤等[73,74].

黄芪桂枝五物汤是《金匮要略》中治疗血痹病的经典方剂, 具有益气温经、和经通痹等功效. 临床试验结果显示, 黄芪桂枝五物汤治疗后化疗患者的神经毒性总发生率明显下降(25%(中药组)*vs*. 63.88%(对照组), $P<0.05$), 使用黄芪桂枝五物汤或加味黄芪桂枝五物汤的患者中医证候明显改善, 生活质量提高[75,76]. CIPN的发生机制包括周围神经结构变化、DNA损伤、线粒体功能障碍、氧化应激增加、离子通道改变和神经炎症激活等[69]. 研究发现, Nrf2可通过减轻氧化应激和抑制TRP蛋白家族表达来保护线粒体功能, 激活Nrf2信号通路可减轻外周神经元损伤和线粒体功能障碍, 从而在改善CIPN中发挥关键作用[77]. 对黄芪桂枝五物汤中的主要药效成分筛选发现, 刺芒柄花素通过与KEAP1结合激活Nrf2-GSTP1信号通路而减轻奥沙利铂诱导的外周神经损伤. GSTP1是Nrf2下游的奥沙利铂代谢酶, 刺芒柄花素具有CIPN保护作用但不影响奥沙利铂的化疗功能[78]. 这些研究提示, 寻找能有效激活Nrf2-GSTP1信号通路的分子可能是预防或治疗CIPN的新策略.

近年研究表明, 外周神经系统中分布的温度敏感瞬时受体电位通道(transient receptor potential channel, TRP channel)在CIPN发生发展中发挥关键作用, 参与CIPN神经性痛觉过敏的形成[79]. 黄芪桂枝五物汤的组分生姜中含有多种TRPV1, TRPA1等离子通道的调节剂, 如6-姜烯酚、8-姜烯酚等[80,81]. 已有研究表明, 6-姜烯酚可通过抑制TRPV1活性减轻小鼠的疼痛性糖尿病神经病变[80]. 因此推测, 黄芪桂枝五物汤也可能通过抑制TRPV1, TRPA1等离子通道缓解CIPN, 发挥神经保护作用. 另有研究证实, 葛根素可通过抑制TRPV1和降钙素基因相关肽等减轻紫杉醇诱导的大鼠周围神经病理性疼痛[82]. 这些研究为临床治疗CIPN提供了新思路.

3.2 中药降低化疗引起的骨髓抑制

骨髓抑制也是化疗所致的主要毒副反应之一, 以外周血中白细胞、红细胞或血小板计数下降为主要表现[83], 中医将其归入“虚劳”“血虚”等范畴, 治疗方法以“扶正”为核心, 或侧重于填精补髓、补益气血、健脾益肾等[84]. 基于数据挖掘的骨髓抑制组方用药规律发现, 单味中药中使用频数较多的药物依次是黄芪、当归、白术、党参、茯苓、甘草、枸杞子、女贞子、熟地黄、鸡血藤[85]. 中药类别则以补虚类为主, 其次是活血化瘀、利水渗湿、清热等. 按照药物归经分类, 则归于肝经、肾经、脾经者最多[85]. 治疗化疗后骨髓抑制的经典方剂主要有四物汤、四君子汤、八珍汤、当归补血汤等.

中药治疗化疗引起的骨髓抑制主要机制有: 促进造血相关因子表达, 促进造血干细胞的增殖以及延缓造血干细胞的衰老. 有研究表明, 当归补血汤与吉西他滨联用可显著减轻吉西他滨所致的骨髓抑制, 增加外周血细胞数量, 提高血小板生成素(thrombopoietin, TPO)和粒细胞-巨噬细胞集落刺激因子(granulocyte macrophage-colony stimulating factor, GM-CSF)的表达, 促进骨髓有核细胞增殖并上调循环相关蛋白[86]. 四物汤、八珍汤可上调促红细胞生成素(erythropoietin, EPO)mRNA表达, 激活不成熟红系细胞, 提高红细胞的数量, 并上调GM-CSF和G-CSF的水平来改善化疗所致的骨髓抑制[87~89]. 另外, 多种中药单体活性成分也被证实有减轻骨髓抑制的作用, 如人参皂苷、黄芪多糖、红景天苷等. 人参皂苷Rg1可提高骨髓单核细胞数量, 提高造血祖细胞集落能力, 并且通过调控Wnt/β-catenin信号通路降低DNA损伤反应, 延缓骨髓间充质细胞和造血干细胞的衰老[90].

3.3 中药降低化疗引起的肝肾毒性

尽管顺铂等化疗药具有出色的抗癌活性, 但其严重的肾毒性和肝毒性也是临床应用受到限制主要原因之一[91]. 临床上常采用滋补肝肾、疏肝理气、清肝利胆等中药联合化疗药来减轻化疗引起的肝肾毒性, 取得了较满意的效果. 自由基的产生是参与顺铂毒性的关键机制之一[92]. 谷胱甘肽(glutathione, GSH)作为自由基清除剂能清除顺铂诱导的自由基, 避免细胞氧化损伤[93]. 谷胱甘肽S转移酶(glutathione S-transferase, GST)通过与谷胱甘肽结合, 在细胞解毒中起关键作用[94]. 升高GSH和GST在保护顺铂引起的肝肾毒性方面发挥重要作用. 研究表明, 一些中药复方, 如琼玉

膏、健脾护肾汤、芪参益气丸、黄葵胶囊、增免抑瘤颗粒等, 能有效减轻化疗引起的肝肾毒性[4,95~101]. 琼玉膏和芪参益气丸能降低顺铂诱导的小鼠血浆尿素氮和肌酐水平, 改善肾小管病变, 减少细胞凋亡, 并加速肾小管细胞再生. 琼玉膏还能显著抑制顺铂介导的肾脏TNF-α, IL-1β mRNA和环氧合酶-2(cyclooxygenase-2, COX-2)蛋白的升高[95,96]. 增免抑瘤颗粒、小柴胡汤、黄连解毒汤等与化疗药联用可防止血清谷丙转氨酶(glutamic-pyruvic transaminase, GPT又称ALT)和门冬氨酸氨基转移酶(aspartate transaminase, AST)水平升高, T-GSH, R-GSH和GST降低以及ICR小鼠的一些组织病理学改变[4,97].

许多中药活性单体, 如葛根素、姜黄素等, 也被证实具有减轻化疗药诱导的肝肾毒性作用[102,103]. 研究表明, 顺铂在体内外均以浓度依赖性方式上调miR-31的水平并影响下游Numb/Notch1信号通路. 葛根素可降低血BUN和SCR水平, 升高血清中GST、超氧化物歧化酶SOD的表达量, 并通过下调miR-31表达抑制Numb/Notch1信号通路, 对顺铂诱导的急性肾损伤起到保护作用[102]. 用姜黄素或α-生育酚预处理可以改善铂类化疗药、阿霉素及甲氨蝶呤诱导的肝损伤, 降低血清ALT和AST水平, 恢复脂质过氧化(lipid peroxidation, LPO)、GSH、非蛋白质硫醇(non-protein thiols, NP-SH)和蛋白羰基(protein carbonyl, PC)的水平, 以及线粒体中抗氧化和呼吸链酶的活性[103~107]. 姜黄素和顺铂联合治疗还可减少顺铂诱导的肾脏细胞空泡化和坏死以及线粒体异常[108,109]. 这些研究为中药改善化疗药引起的肝肾毒性提供了科学依据.

3.4　中药降低化疗引起的胃肠道反应

胃肠道副反应包括食欲不振、腹泻、恶心和呕吐, 是癌症患者放化疗后最常见的症状. 中医认为, 化疗药药性较烈, 往往会损伤脾胃, 使脾胃运化不畅, 气血生化不足, 从而加剧人体正气亏虚, 在脾胃上表现为脾胃气虚, 气机不畅, 痰瘀互结[110]. 临床上常以益气和胃、养益气血、燥湿化痰方法改善患者的胃肠道系统功能, 高频使用的中药有半夏、甘草、茯苓、白术、陈皮, 以性温、味甘、归属脾胃经的药物使用最多[111]. 半夏泻心汤对化疗药导致的腹泻、呕吐等具有较好的疗效[112,113], 研究发现, 其可通过抗炎、抗氧化(降低组织炎症因子如TNF-α, IL-1β, IL-17, IL-23等的水平, 提高SOD活性及Nrf2的表达)作用改善溃疡性结直肠炎状况[114]. 中药活性成分木犀草素可通过激活Nrf2信号通路保护氧化应激诱导的细胞损伤, 进而预防化疗诱导的结直肠炎的发生[115].

经典名方六君子汤在我国和日本广泛用于治疗功能性消化不良、胃食管反流以及癌症患者化疗引起的消化不良. 研究发现, 六君子汤作为一种胃饥饿素激动剂可有效治疗顺铂等化疗药引起的消化不良和癌症厌食-恶病质综合征[116,117], 还能显著改善接受近端胃切除术的胃癌患者的胃肠道不适症状和长期生活质量[118]. PHY906源自黄芩汤的配方, 由四种中药组成: 甘草、芍药、黄芩和大枣. 一些临床研究表明, PHY906可提高伊立替康、5-氟尿嘧啶(5-fluorouracil, 5-FU)和卡培他滨等广谱抗癌药物在结直肠癌、肝癌和胰腺癌中的治疗指数, 增强化疗药的抗肿瘤活性, 降低胃肠道毒性, 如腹泻、腹部绞痛和呕吐等, 但不影响化疗药的药代动力学特性[119~122]. 机制研究发现, PHY906通过促进肠道祖细胞或干细胞的再生并增强Wnt信号通路中Wnt3a的活性而恢复肠道上皮成分. 此外, PHY906还可通过减少中性粒细胞或巨噬细胞的浸润、肠道中TNF-α的表达以及血浆促炎因子的浓度而发挥抗炎作用[123,124]. 中药大多是口服用药, 进入胃肠道会与微生物发生相互作用. 研究发现, 中药干预可以改善大肠癌患者术后或化疗引起的肠道微生态失衡状况, 抑制有害菌, 促进有益菌的生长, 使肠道微生物群落的丰富程度和多样性增加, 进而对机体产生相应的影响, 降低化疗引起的胃肠道毒性[125,126].

4　总结与展望

中药作为一种补充和替代疗法对癌症治疗有重要影响. 在癌症治疗中, 中药结合化学疗法、免疫疗法和靶向疗法能显著增强这些疗法的抗肿瘤效果, 并减少它们引起的毒副作用和并发症. 表1和表2总结了临床上常用的中药抗肿瘤增效减毒的中成药或中药方剂及其应用. 中药成分多样、机制复杂, 在疾病治疗上具有整体性、系统性, 不局限于疾病本身, 更重视机体整体健康水平; 在生理上以脏腑经络、气血津液为基础, 主张阴阳平衡, 气血通畅; 在治疗方法上以辨证施治为特点, 重视个体差异和病证演变; 在方药上根据药物性味归经, 运用七情和合的配伍法则制定方剂, 对于重大疾

表 1 临床上常用于肿瘤治疗增效减毒的代表性中成药或中药方剂

Table 1 Representative traditional Chinese medicine preparations commonly used in clinical cancer treatment to enhance efficacy and reduce toxicity

复方名称	复方组成	功用	增强抗肿瘤活性的临床证据	参考文献
参芪扶正注射液	党参、黄芪	益气扶正	与化疗药联用可显著提高肿瘤治疗总体有效率, 提高患者免疫力, 降低化疗引起的恶心、呕吐、口腔黏膜炎和白细胞减少等毒副反应	[24,25]
康莱特注射液	薏苡仁油	益气养阴, 消癥散结	与化疗药联用可显著提高肿瘤治疗总体有效率, 提高患者免疫力, 提高生存质量, 降低化疗引起的毒副反应	[26~28]
华蟾素注射液	蟾酥提取物	解毒, 消肿, 止痛. 用于中、晚期肿瘤	与化疗药联用可提高肿瘤客观反应率和疾病控制率, 提高患者1~2年生存率和生活质量, 减轻中性粒细胞减少症、血小板减少症、恶心、呕吐、贫血、肝损伤、肾损伤和脱发	[29~31]
鸦胆子油乳剂注射液	鸦胆子油	用于肺癌, 肺癌脑转移及消化道肿瘤	与化疗药联用可显著提高NSCLC和胃癌治疗的总体有效率, 提高患者生存质量, 降低化疗引起的骨髓抑制, 中性粒细胞减少, 血小板减少, 肝损伤等	[32,33]
消癌平注射液	通关藤	清热解毒, 化痰软坚. 用于食道癌、胃癌、肺癌等, 并可配合放、化疗辅助治疗	与EGFR-TKI或铂类化疗药联用可提高晚期NSCLC患者的客观反应率, 延长无进展生存期, 减少贫血、白细胞减少症、血小板减少症、恶心、呕吐等不良反应的发生	[64,127]
黄芩汤(PHY906)	甘草、芍药、黄芩和大枣	清热止痢, 和中止痛	可通过提高卡培他滨等化疗药的抗肿瘤活性和降低其在晚期肝癌/胰腺癌中的毒性来增加其治疗指数, 并能减轻化疗引起的呕吐、腹泻等胃肠道反应	[121~123]

表 2 临床上常用于抗肿瘤治疗减毒的代表性中成药或中药方剂

Table 2 Representative traditional Chinese medicine preparations commonly used in clinical cancer treatment to reduce toxicity

复方名称	复方组成	功用	抗肿瘤治疗减毒的临床证据	参考文献
黄芪桂枝五物汤	黄芪、桂枝、芍药、生姜、大枣	血痹. 肌肤麻木不仁, 脉微涩而紧	降低铂类等化疗药引起的外周神经毒性	[75,76]
温经和血通痹方	黄芪、川芎、当归、赤芍、桂枝、鸡血藤、活血藤、威灵仙、丹参、路路通、牛膝、甘草	温经, 活血, 通络	通过内服外用可治疗气血亏虚型患者奥沙利铂化疗所致的周围神经毒性	[74]
当归补血汤	黄芪、当归	补气生血	减少化疗药引起的骨髓抑制, 增加外周血细胞数量, 提高TPO和GM-CSF的表达, 促进骨髓有核细胞增殖	[86]
八珍汤	人参、白术、白茯苓、当归、川芎、白芍药、熟地黄、甘草	益气补血	减少化疗药引起的骨髓抑制, 减少化疗过程中升白细胞及升血小板药物的使用量	[88,89]
健脾护肾汤	黄芪、生地黄、丹参、党参、白术、川芎、当归	活血化瘀, 护肾健脾	缓解顺铂化疗引起的患者体内氧化应激及炎症反应, 改善患者肾功能	[98,99]
黄葵胶囊	黄蜀葵花	清利湿热, 解毒消肿	对顺铂化疗导致的肾功能损伤有保护作用, 降低的血肌酐、胱抑素C等水平, 减轻顺铂的肾毒性	[100,101]
半夏泻心汤	半夏、黄连、黄芩、干姜、甘草、大枣、人参	寒热平调, 消痞散结	对化疗所致的迟发性腹泻有预防和控制作用, 并能减轻恶心、呕吐等胃肠道反应	[112,113]
六君子汤(Rikkunshito)	党参、白术、茯苓、甘草、陈皮、半夏	益气健脾, 燥湿化痰	对顺铂或紫杉醇化疗引起的恶心、呕吐和厌食症有预防作用	[116~118]

病的预防和治疗具有优势.

近年来, 大量研究发现中药复方或单体可以通过作用于耐药相关信号通路、药物外排泵的表达、DNA损伤修复以及重塑肠道菌群等增强肿瘤细胞对化疗药物的敏感性[19~22]; 通过调控免疫检查点的表达水平, 或对免疫系统重编程, 解除肿瘤微环境的免疫

抑制状态, 增强免疫检查点抑制剂的抗肿瘤疗效[39~49]; 通过作用于旁路或下游信号通路如STAT3逆转EGFR-TKI耐药, 增强肿瘤细胞对靶向药的敏感性[57~65]. 除了增敏, 中药对于西药抗肿瘤诱发的毒副作用减毒方面也取得了显著成效. 许多临床和基础研究表明, 中药复方或单体通过激活Nrf2信号通路减轻外周神经元损伤和线粒体功能障碍, 或作用于离子通道, 降低炎症因子水平等缓解化疗药引起的外周神经毒性[77~82]; 通过促进造血相关因子表达, 促进造血干细胞增殖以及延缓造血干细胞衰老等降低化疗引起的骨髓抑制[86~90]; 通过清除自由基, 保护线粒体功能, 避免细胞氧化损伤等降低化疗药诱发的肝肾毒性[95~109]; 通过促进胃饥饿素生成、抗炎、保护胃肠道屏障、重塑肠道菌群等降低西药抗肿瘤引起的食欲不振、腹泻、呕吐等胃肠道副反应[114~124].

虽然中药在弥补现代医学的不足中显现出了优势, 对西药抗肿瘤有明显的增效和减毒作用, 通过复方用药还有助于提高临床综合疗效, 而且价格较低能缓解部分患者的家庭经济负担, 改善患者生存质量. 但是, 中医药在防治重大疾病中也存在很多问题, 如成分复杂, 难以进行严格的质量控制; 缺乏大样本、高质量的临床试验疗效证据支持; 体内药代动力学过程及药效机制研究不足等. 本文建议从以下几方面加强中西医结合抗肿瘤的研究.

(1) 加强中药质量控制研究. 从新型标准物质发现、中药质量等级评价以及中药中有毒有害物质风险评价等方面展开. 标准物质对于确定中药的真伪、评价其质量优劣极其重要, 而部分对照品存在不稳定、毒性高等问题, 而且采用单一对照品评价中药质量不符合中医强调的整体理论. 因此, 建议开展替代标准物质、中药对照制剂和数字标准物质等研究工作. 构建以质量与安全为核心的质量等级评价模式, 替代现有的仅根据产地、重量、大小等因素的中药材质量等级评价模式. 加强中药中多糖、有毒有害物质的识别与检测, 建立完善动物类中药、发酵类中药的质控标准等[128].

(2) 提升中西医结合抗肿瘤的临床证据质量. 中医药对于重大疾病的防治疗效多局限于临床疗效观察或临床经验总结, 缺乏以大样本、多中心、随机、双盲等为原则的高质量临床试验数据分析支持. 而且中医辨证施治的特点导致临床试验设计难以使用统一的标准对疗效和诊断进行严格的统计评价. 建议通过人工智能等大数据方法对中医临床诊断和疗效进行客观化归类分析, 严格依据国际规范进行中医药防治疾病的临床试验设计、注册、实施和报告, 建立健全中医药临床数据共享机制, 进一步强化中医药的循证研究, 提升中医药或中西医结合防治重大疾病的临床研究证据水平.

(3) 加强中西医结合抗肿瘤的药效物质基础与机制研究. 中药复方具有多靶点、多成分、整体性特点, 系统阐明中药或中西医结合治疗重大疾病的药效物质和整体性作用机制, 有助于揭示中药复方科学内涵, 发现药物靶标, 指导中药新药研发, 传承和发展中医药理论. 建议建立中药复方的定性, 定量特征指纹图谱, 归总候选药效物质成分, 通过活性评价及药效物质筛选, 建立成分-物质-药效系统网络. 基于药效物质基础, 通过代谢组学、蛋白组学、网络药理学等技术手段筛选药效靶标, 然后通过基因编辑、结构生物学等方法对靶点进行验证, 构建成分-靶点-通路的互作网络, 为复方中药的现代临床应用提供科学依据.

(4) 组方配伍规律及组分中药的研究. 基于数据挖掘技术进行复方中药的重构与分析, 结合疾病、证候特征等阐明并总结中药的组方配伍规律, 利用已有的方剂数据对临床实践进行指导, 提高临床诊疗效果, 并通过用药规律分析, 为中药新药的研发提供依据和指导. 然后在中药药效物质和作用机理研究的基础上, 针对临床特定病症, 以系统科学思想为指导, 遵循传统配伍理论与原则, 通过药化、药理、药物信息学等多学科技术手段, 强化主效应, 减轻或避免副效应, 形成组效关系明确的中药组分配伍形式, 推动中药的现代化及精准化进程.

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Advances in the synergistic and toxic attenuating effect of traditional Chinese medicine in cancer treatment

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Chemotherapy, targeted therapy and immunotherapy are the main pharmacotherapies for the treatment of malignant tumors. However, side effects and drug resistance are the key reasons that limit the efficacy of anti-tumor drugs. Traditional Chinese medicine is an important part of complementary and alternative medicine. It can not only prevent the occurrence and development of tumors, improve the anti-tumor efficacy of western medicine, but also attenuate the toxic and side effects of western anti-tumor medicine and improve the patients' quality of life. In this paper, the advances in anti-tumor research of integrated traditional Chinese and western medicine are reviewed from the aspects of sensitization and synergistic effect, reversal of drug resistance, enhancement of immune response and reduction of toxic and side effects on normal tissues and organs, and a new approach of reducing toxicity and increasing efficacy of western anti-tumor medicine is proposed. However, many problems remain in the clinical application of traditional Chinese medicine in the prevention and treatment of malignant tumors and other serious diseases, such as complex ingredients and lack of strict quality control; lack of efficacy evidence support from high-quality clinical trials with large sample sizes; insufficient research on the pharmacodynamic materials and mechanisms. At the end of this paper, we provide an outlook for the research direction of integrated Chinese and western medicine for anti-tumor purposes, with an attempt to reveal the scientific connotation of traditional Chinese medicine in the prevention and treatment of major diseases, and to inherit and develop traditional Chinese medicine theories.

traditional Chinese medicine, integrated traditional Chinese and western medicine, cancer, synergistic effect, toxic attenuating effect

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