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封面故事

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述评 EDITORIAL

MSS型mCRC的免疫治疗策略及中医药研究探索

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Immunotherapy strategies and traditional Chinese medicine treatment for microsatellite stable metastatic colorectal cancer

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Abstract

The incidence and mortality of colorectal cancer (CRC) have increased year by year. In addition to traditional radiotherapy, chemotherapy, and targeted therapy, immunotherapy also brings hope to more patients with metastatic colorectal cancer (mCRC). However, these treatments are limited to patients with high microsatellite instability, and about 95% of mCRC patients with microsatellite stability (MSS) can not benefit from them. How to enhance the response of MSS mCRC patients to immunotherapy is the focus of current research. In recent years, it has been found that immunotherapy strategies are expected to improve the clinical efficacy for such patients, and the research reports of TCM combined with immunotherapy are increasing day by day. Therefore, this article aims to review the immunotherapy and traditional Chinese medicine treatment for MSS colorectal cancer.

Key Words: Colorectal cancer; Microsatellite stable; Immunotherapy; Traditional Chinese medicine

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摘要

结直肠癌(colorectal cancer, CRC)发病率和死亡率逐年上升, 除传统的放疗、化疗、靶向治疗模式外, 免疫治疗也为更多转移性结直肠癌患者带来希望, 但这仅限于对高微卫星不稳定型的患者, 对约占95%的微卫星稳定(microsatellite stable, MSS)型的转移性结直肠癌(metastatic colorectal cancer, mCRC)患者尚不能从中获益, 如何增强MSS型mCRC患者对免疫治疗的应答是当前研究的热点. 近年来研究发现免疫治疗的联合策略有望改善此类患者的临床疗效, 中医药联合免疫治疗的研究报道日趋增多. 因此, 本文旨在对MSS型结直肠癌的免疫治疗和中医药研究进行综述.

关键词: 结直肠癌; 微卫星稳定; 免疫治疗; 中医药

核心提要: 微卫星稳定(microsatellite stable, MSS)型转移性结直肠癌(metastatic colorectal cancer, mCRC)对单一免疫检查点抑制剂基本无效, 通过联合免疫治疗或探索新的疗效预测标志物有可能提高MSS型mCRC的临床疗效. 本文旨在对MSS型结直肠癌的免疫治疗和中医药研究进行综述.

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0 引言

全球结直肠癌发病呈上升趋势. 2020年约4.20%的癌症相关死亡是由结直肠癌引起的[1]. 目前, 我国CRC的防控形势也不容乐观, 发病人数和死亡人数均呈增长趋势[2], 且发病率和死亡率高于全球平均水平[3].

尽管手术、化疗、放疗和分子靶向治疗等常规治疗发展迅速, 但mCRC总体疗效并不乐观, 平均中位生存时间仅30 mo左右[4]. 近年来, 以免疫检查点抑制剂(immune checkpoint inhibitor, ICI)为主的肿瘤免疫治疗给mCRC带来新希望. 遗憾的是, 占绝大多数(约95%)的DNA错配修复正常/微卫星稳定(pMMR/MSS)型CRC患者并不能从中获益[5], 故被称为“冷肿瘤”. 因此, 如何提高MSS型mCRC中免疫应答, 从而改善其临床预后已经成为临床的难点、热点问题.

1 免疫治疗

免疫治疗是通过肿瘤浸润淋巴细胞(tumor infiltrating lymphocytes, TIL)在肿瘤微环境(tumor mircroenvirment, TME)中起免疫调节作用, 从而影响肿瘤进展, 与肿瘤细胞的免疫逃逸密切相关. 其目标是启动宿主免疫系统, 以提供针对恶性肿瘤的被动或主动免疫. 免疫疗法旨在增强自身免疫系统以清除恶性细胞, 对多种癌症类型免疫治疗显示出持续的临床反应[6-8]. 特别是近年来, 包括程序性死亡受体1(programmed death receptor1, PD-1)/细胞程序性死亡-配体1(programmed cell death 1 ligand 1, PD-L1)抑制剂的ICI联合治疗在临床研究中初步展现了较好的疗效和安全性[9-11], 开启了肿瘤治疗的新时代. 但对于pMMR/MSS型CRC鲜有疗效.

MSS型CRC对PD-1/PD-L1抑制剂低响应, 除了因肿瘤抗原呈递不足而难以被免疫系统识别外, 还与TIME中的T细胞、骨髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)、巨噬细胞等密切相关[12], 越来越多的研究发现多种治疗方法联合能够提高PD-1抑制剂在MSS型CRC中的响应率.

2 MSS型mCRC的免疫联合治疗策略

2.1 免疫治疗联合分子靶向治疗 免疫联合靶向治疗是指将免疫治疗与分子靶向治疗结合起来, 通过协同作用来增强抗肿瘤效应. 其原理是通过靶向治疗抑制肿瘤生长和转移, 同时通过免疫治疗激活机体免疫系统, 增强对肿瘤的免疫应答. 总结如表1.

2.1.1 联合抗EGFR药物: 抗表皮生长因子受体(epithelial growth factor receptor, EGFR)药物是RAS野生型mCRC患者一线治疗的标准方案, 通过抑制EGFR介导的肿瘤细胞生长, 并诱导免疫原性细胞死亡达到抗肿瘤效果. 有临床前研究显示抗EGFR治疗能引起肿瘤特异性免疫反应和免疫原性细胞凋亡, 免疫治疗联合抗EGFR治疗可能增强抗肿瘤效应[13]. 西妥昔单抗具有最高的刺激抗体依赖性细胞介导的细胞毒性的能力. 2021年公布的一项多中心、单臂的Ⅱ期临床试验讨论了阿维单抗+西妥昔单抗治疗RAS野生型mCRC患者的治疗效果, 在纳入的71例MSS型mCRC患者中, 中位总生存期(median overall survival, mOS)为11.6 mo, 中位无进展生存期(median progression-free survival, mPFS)为3.6 mo[14]. 另外, 联合西妥昔单抗及化疗一线治疗MSS RAS/BRAF野生型 mCRC的临床试验结果显示ORR为50%, 中位无进展生存期为7.2 mo[15]. 以上研究显示了免疫治疗联合抗EGFR药物的良好临床应用前景.

2.1.2 联合抗VEGF药物: 抗血管内皮生长因子(vascular endothelial growth factor, VEGF)药物主要是以VEGF为作用靶点, 通过抑制其表达而达到抑制肿瘤细胞生长和转移的作用. 2021年进行的一项临床试验对化疗和贝伐珠单抗联合或不联合atezolizumab治疗

表 1 免疫治疗联合分子靶向治疗

研究类型	入组患者	治疗方案	总缓解率	中位无进展生存期
免疫治疗+抗EGFR药物	RAS WT MSS型mCRC	阿维+西妥昔	8.50%	3.6 m
	RAS WT型mCRC	阿维+西妥昔	50%	7.2 m
免疫治疗+抗VEGF药物	MSS型mCRC	阿替利珠+贝伐珠	59%	13.1 m
免疫治疗+TKI	MSS型mCRC	纳武利尤+瑞戈非尼	33.30%	6.3 m
	MSS型mCRC	阿维+瑞戈非尼	/	3.6 m

EGFR: 抗表皮生长因子受体; VEGF: 抗血管内皮生长因子; TKI: 酪氨酸激酶抑制剂.

mCRC的疗效进行了比较和评估, 结果显示在199例MSS型mCRC患者中, 联合治疗组的无进展生存期(progression-free survival, PFS)大于未联合治疗组[16], 表明免疫治疗联合抗VEGF药物能增强免疫治疗的抗肿瘤效果.

2.1.3 联合酪氨酸激酶抑制剂: 酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)通过阻断酪氨酸激酶的活性, 抑制细胞增殖, 发挥抗肿瘤效应[17]. 特别是多靶点的TKI, 如瑞戈非尼、呋喹替尼等, 靶点更加广泛. 研究发现瑞戈非尼除具有抗血管生成效应, 还能够进一步抑制CSF-1通路, 通过阻断CSF-1通路影响肿瘤微环境中的M2型巨噬细胞[18], 增强了肿瘤免疫相关的吞噬作用, 从而进一步提高抗肿瘤的免疫活性, 逆转免疫治疗的耐药, 这为联合免疫的治疗带来可能. REGONIVO研究纳入了25例均接受过治疗两种化疗方案的结直肠癌患者, 予以瑞戈非尼联合纳武利尤单抗治疗, 研究结果显示, 瑞戈非尼80 mg加纳武利尤单抗的联合治疗方案具有可控的安全性和较好的抗肿瘤活性. 在排除1例MSI-H的CRC患者后, MSS型CRC患者的ORR为33.3%, PFS约为6.3 mo[19]. REGOMUNE试验评估了瑞戈非尼联合PD-L1抑制剂avelumab治疗48例MSS型mCRC患者的疗效和安全性. 研究结果显示, 该联合治疗方案在微卫星稳定结直肠癌患者中表现出了一定的疗效, 中位无进展生存期为3.6 mo, 中位总生存期为10.8 mo. 研究表明, 与瑞戈非尼单药治疗相比, 该联合治疗方案的疗效更好[20].

2.2 联合化疗 目前结直肠癌的化疗药物以氟尿嘧啶类的氟尿嘧啶、卡培他滨, 铂类的奥沙利铂和喜树碱类的伊立替康三类药为主. 研究表明[21], 这些药物能通过影响肿瘤细胞的核酸和蛋白质结构与功能, 直接抑制肿瘤细胞增殖或诱导细胞凋亡. KEYNOTE-651研究对帕博利珠单抗同步联合标准用法的一线mFOLFOX7或二线FOLFIRI方案治疗mCRC的疗效和预后进行了长期随访, 结果显示帕博利珠单抗联合mFOLFOX7方案的ORR为58.1%, 帕博利珠单抗联合FOLFIRI方案的ORR为15.6%, 值得进一步研究.

2.3 联合放疗 放射治疗通过多种机制增加其免疫协同的作用. 一方面, 放疗引发细胞损伤以激活细胞保护机制, 通过损伤细胞内DNA和其他细胞成分以触发一系列细胞保护反应; 另一方面, 放疗可以激活临床可行的信号通路, 并通过靶向抗癌治疗来提高临床疗效[22]. VOLTAGE研究是第一个随机接受新辅助放化疗(卡培他滨+50.4 Gy)和纳武利尤单抗免疫治疗局部晚期CRC的患者的研究. 结果显示, 37例MSS型结直肠癌患者中有11例达到病理完全缓解(pathologic complete response, PCR)[23]. AVANA研究是一项关于局部晚期直肠癌术前放化疗联合avelumab的多中心 II 期研究, 显示22例(23%)患者实现了PCR且59例(61.5%)患者达到了主要病理反应. 观察到主要的病理反应. 新辅助放化疗(neoadjuvant chemoradiotherapy, NCRT)和avelumab的联合使用进一步增加了PD-L1在肿瘤细胞中的表达, 因此, NCRT和免疫检查点抑制剂的联合使用非常有价值[24].

2.4 联合双特异性抗体 双特异性抗体(bispecific antibody, BsAb)是指能同时特异性结合两个抗原或抗原表位的人工抗体, 通常通过细胞融合或重组DNA技术制备而成. 双特异性抗体能增强对肿瘤细胞的杀伤力, 影响肿瘤细胞的生长增殖及存活, 或增强与肿瘤细胞的特异性结合并直接杀伤肿瘤细胞.

LY6G6D是位于6号染色体主要组织相容性复合体(major histocompatibility complex, MHC)III类区域的白细胞抗原簇, 由于其在MSS中的高表达及其在正常组织和其他肿瘤类型中的低表达, 被鉴定为肿瘤选择性表达的CRC抗原[25-27]. 优化的LY6G6D-TDB靶向LY6G6D的膜近端表位, 并以高亲和力与CD3结合, 在体外和体内均表现出强大的抗肿瘤活性. 在小鼠异种移植肿瘤模型中, LY6G6D-TDB作为单一药物对已建立的结直肠肿瘤表现出抗肿瘤功效, 当LY6G6D-TDB与PD-1阻断剂联合使用时, 可以实现增强的疗效[28].

3 MSS型mCRC的免疫治疗预测性标志物

由于各个临床试验的样本量较小, 目前对于MSS型结直肠癌免疫治疗相关的预测潜在生物标志物或临床病理

特征尚未形成共识, 但学者们仍认为精准人群的筛选更有利于肿瘤治疗.

3.1 POLE/POLD基因突变 结直肠癌发生POLE/POLD1的突变概率约为7.37%, 且多见于MSS型结直肠癌. 研究表明, 携带POLE/POLD1基因突变的患者, 其肿瘤突变负荷(tumor mutation burden, TMB)显著高于未携带者. 徐瑞华团队研究发现, POLE/POLD1基因突变是非常有潜力的免疫治疗独立标志物, 且不限癌种, 对于癌种中检测为MSS的患者群体将会有很大的应用意义[29].

3.2 TMB状态 TMB即肿瘤突变负荷, 是指肿瘤基因组中去除胚系突变后的体细胞突变数量. 有专家认为高TMB联合免疫治疗具有更好的抗肿瘤效果, 2021年的一项回顾性随访了157名高TMB患者, 结果显示单独接受化疗和单独接受免疫治疗的患者, 其PFS分别为6.75 mo和24.2 mo, 表明TMB或可作为疗效预测标志物而使用[30]. 但也有研究结果显示对于MSS型mCRC患者来说, TMB对OS的影响不如其他标志物(如BRAF)强, 其与直接治疗的相关性仍有待确定[31,32].

3.3 肿瘤转移部位 肿瘤转移是导致患者死亡的主要原因, 肝脏则是最常发生转移的器官之一[33]. 新近研究发现, 肝脏微环境中肿瘤相关的巨噬细胞诱导癌细胞和肝细胞分泌FGL1升高, 从而通过抑制T细胞的浸润以实现CRC转移[34]. 因此肝转移或许可以作为独立因素预测免疫治疗的响应情况. 有研究表明[35,36], 相较于具有其他器官转移的癌症患者, 具有肝转移的患者对于免疫治疗的应答率更低、患者生存期更短, 其机制可能与肝脏免疫微环境中巨噬细胞亚群诱导CD8T细胞凋亡或树突状细胞(dendritic cell, DC)有关.

3.4 肿瘤浸润性淋巴细胞 肿瘤浸润性淋巴细胞(tumor infiltrating lymphocytes, TILs)是免疫治疗过程中最重要的效应细胞类型. 在上世纪, 就有学者提出TILs可作为判断结直肠癌预后的一个独立因素, 且优于Dukes分期. 近年来, 多个团队运用现代技术如免疫组化、HE染色等对TILs进行研究, 均显示其在中期结直肠癌中的预后预测价值甚至高于TNM分期及MSI状态, 有实验表明CD8和CD45RO的高表达与Ⅱ期CRC的更佳疾病结局和更好的长期癌症特异性生存相关[37,38].

3.5 循环肿瘤DNA 循环肿瘤DNA(ctDNA)是一种由肿瘤细胞释放到血液中从而随血液全身循环的DNA, 能携带来源于肿瘤细胞相关的遗传学特征. 2022-06-04, 《新英格兰杂志》发表了一项关于结直肠癌的随机对照试验, 研究结果表明, ctRNA指导下的辅助化疗策略可以在不影响患者总体无复发生存期的前提下, 降低接近50%(从28%降低至15%)的术后辅助化疗率, 避免了相当一部分患者的无效化疗[39]. 新近研究显示, 在49例结肠癌术后患者中, 免疫评分高的患者, 其ctDNA阳性率普遍较低, 表明他们最有资格接受无化疗治疗[40].

4 中医药协同免疫治疗的探索

4.1 中医药调节免疫代谢重编程 代谢重编程被认为是恶性肿瘤的标志性特征. 在各种压力刺激之下, 代谢产物的环境随着代谢途径一起改变的现象, 被称为代谢重编程. 肿瘤细胞为满足其快速增殖的生物能量和生物合成需求, 并适应肿瘤微环境, 能量代谢模式会相应进行重编程, 主要体现在葡萄糖、脂质、氨基酸代谢的异常. 由于乳酸脱氢酶[41]、线粒体TNF受体关联蛋白[42]、转录调控因子[43]等的参与, 结直肠癌的肿瘤细胞和免疫细胞也发生了代谢途径的重编程. 王建华[44]通过复方肠泰制剂诱导结直肠癌细胞发生自噬, 从而促进肿瘤相关的巨噬细胞向M1极化以发挥抗肿瘤效果; 结果显示, 与对照组相比, 复方肠泰治疗组的小鼠质量与小鼠体积均受到明显抑制. 刘宗瑜等[45]将养正消积胶囊用于治疗结直肠癌, 结果显示结直肠癌中的NK细胞数量得到了显著提高, 明显改善了结直肠癌患者的生活质量. 多种研究表明, 中医药可以通过调控免疫代谢重编程, 改善免疫状态, 从而进一步增强抗肿瘤效果.

4.2 中医药调节肠道菌群 肠道菌群可通过多种方式使结直肠癌发生改变, 如失调菌群激活“炎-癌”转化信号通路[46]、刺激炎症因子的产生以抑制免疫微环境[47]、通过细菌来源的基因毒素影响细胞DNA[48]等. 王楠等[49]研究发现, 葛根芩连汤(GQD)能下调结肠癌模型大鼠肠道大肠埃希菌、肠球菌数量, 上调乳酸杆菌及双歧杆菌数量, 且同时Wnt/β-catenin通路蛋白表达降低, 提示GQD调控Wnt/β-catenin通路可减轻肠道炎症反应. 王布江等[50]的研究也同样验证了这一观点, 他们通过实验发现GQD能减轻大鼠结直肠癌所致的病理损伤, 调节血清脂肪酶、白细胞介素-6、细胞介素-10及肿瘤坏死因子-炎性指标, 明显降低结肠内容物中肠球菌和大肠埃希菌含量, 提高双歧杆菌和乳酸杆菌含量. Cai等[51]研究者通过实验发现参芪益肠颗粒可纠正CRC荷瘤小鼠肠道菌群的紊乱状态, 并初步探索出其抗肿瘤作用可能与调控PI3K/Akt/mTOR信号通路相关. 多种研究结果显示, 中医药可以通过调节肠道菌群起到抗肿瘤效果, 干预结直肠癌的发生发展.

4.3 中医药联合免疫检查点抑制剂 目前, 中医药联合免疫检查点抑制剂治疗结肠癌的研究相对较少, 但我们仍可以从一些肿瘤相关的研究中探寻到未来MSS型mCRC的治疗之路. 王冰冰等[52]纳入初次使用免疫检查点抑制剂治疗的中晚期恶性肿瘤患者60名, 根据是否使用中药分成中药组和对照组, 其中中药组44人, 对照组16人. 通

过受试者曲线(receiver operating characteristic curve, ROC)对联合中药变量进行分析, 结果显示联合中药的曲线下面积(area under curve, AUC)为0.699, 表明中医药对于免疫检查点抑制剂使用的疗效有预测价值. 2021年进行的一项研究发现大黄附子败酱汤(DFB)能抑制CCL2并保留祖细胞末端耗竭的T细胞, 通过调节适应性免疫来防止肿瘤进展[53]. 新近研究表明[54], 通关藤提取物(MTE)抑制结CRC细胞系HCT116和LoVo中TGF-β1和PD-L1的表达, 从而抑制癌细胞的免疫逃逸. 另外, 在MC38小鼠结直肠癌中发现丹参水浸泡(SMAE)通过调节Cox1/PGE2级联反应与抗PD-L2协同治疗并减弱了TAM对肿瘤的浸润, 直接证明中医药联合免疫治疗能起到更佳的抗肿瘤效果[55].

5 结论

MSS型mCRC作为一种对免疫检查点抑制剂不敏感的“冷肿瘤”, 其免疫治疗之路近年来已有所进展, 虽进程较缓慢, 但多项临床试验正在积极探索中. 目前, 相关数据的正确和准确仍需反复验证, 进行对应的早期试验, 以夯实免疫联合治疗策略的有效性. 与此同时, 加强对生物分子标志物的探索和中医药的临床和基础研究, 进一步加强转化性研究. MSS型结直肠癌免疫联合治疗之路值得期待.

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