·综 述　General review·

肝动脉灌注化疗联合系统治疗在原发性肝癌中的研究进展

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【摘要】 原发性肝癌是常见的恶性肿瘤之一，肝动脉灌注化疗（HAIC）和系统治疗是中晚期肝癌主要的治疗方式。HAIC通过方案及介入技术的改进，能够有效控制肝内病灶且安全性好。系统治疗从单一的靶向药物或免疫治疗进入靶免联合的时代，治疗手段日益丰富。但无论是HAIC或系统治疗，单一治疗效果有限。近年来，HAIC联合系统治疗能有效提高客观缓解率、延长无进展生存时间、增加转化切除机会。但对于长期生存获益、选择最优联合方案、筛选合适的目标人群等问题的解决仍需积累临床经验。当前证据表明，HAIC联合索拉非尼对于肝癌合并门静脉主干癌栓疗效确切，联合仑伐替尼或免疫治疗仍需探索，联合免疫及靶向治疗是未来一线治疗的潜在选择。

【关键词】 原发性肝癌；肝动脉灌注化疗；分子靶向治疗；免疫治疗

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Research progress in hepatic arterial infusion chemotherapy combined with systemic therapy for the treatment of primary hepatocellular carcinoma

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【**Abstract**】 Primary hepatocellular carcinoma (HCC) is one of the common malignant tumors. Hepatic artery infusion chemotherapy (HAIC) and systemic therapy are important treatment options for medium-advanced HCC. With the improvement of chemotherapy scheme and interventional technology, HAIC has been able to effectively control the intrahepatic lesions with good safety. Systemic therapy, which originally adopted single targeted drug or immunotherapy, has already entered a new era characterized by targeted therapy combined with immunotherapy, and the treatment methods are becoming more and more. But, the efficacy of single therapy, regardless of HAIC therapy or systematic therapy, is limited. In recent years, HAIC combined with systemic therapy has achieved certain effectiveness in improving objective remission rate, prolonging progression-free survival, and increasing the opportunity of transformation resection. However, more clinical experience needs to be accumulated before some important issues such as the long-term survival benefits, the selection of optimal combination scheme, the screening of suitable target population, etc. can be solved. Current evidences show that HAIC combined with sorafenib carries reliable effect for HCC complicated by main portal vein tumor thrombus, but HAIC combined with lenvatinib or immunotherapy still needs to be further studied. HAIC combined with immunotherapy and targeted therapy is a potential option for future first-line therapy.

【**Key words**】 primary hepatocellular carcinoma; hepatic artery infusion chemotherapy; molecular targeted therapy; immunotherapy

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2020年世界卫生组织的数据表明，肝癌的病死率排名第3[1]。我国约有60%的肝癌患者被确诊时已经为中晚期，失去了外科手术机会[2]。目前，系统治疗（分子靶向治疗和免疫治疗）和局部治疗[肝动脉栓塞术、肝动脉灌注化疗（hepatic arterial infusion chemotherapy，HAIC）]是中晚期肝癌主要的治疗选择。单一系统治疗或者局部治疗效果有限，客观缓解率较低，生存获益不佳[3-7]。以HAIC为代表的局部介入治疗，可提高肝脏局部治疗效果并减轻不良反应[8]。特别是基于HAIC-FOLFOX（奥沙利铂、氟尿嘧啶、亚叶酸钙）灌注化疗方案联合系统治疗展示了良好的抗肿瘤效果。本文重点介绍HAIC联合系统治疗治疗肝癌的新进展，为临床选择联合治疗方式提供参考。

1 HAIC联合分子靶向药物

1.1 HAIC联合索拉非尼

索拉非尼是一种多激酶抑制剂，可阻断肿瘤细胞增殖和血管生成，通过抑制丝氨酸/苏氨酸激酶以及VEGFR-2、VEGFR-3、PDGFR-β cKIT、FLT-3，诱导肿瘤细胞凋亡[9]。两项Ⅲ期试验表明，索拉非尼比安慰剂显著延长总生存期（OS）[9,10]。索拉非尼因此成为晚期肝癌的治疗选择，HAIC与索拉非尼联合治疗的短期疗效优势明显，但在生存率和不良反应方面获益不一[8]。

Ikeda等[11]的研究显示，HAIC（顺铂）加索拉非尼疗效好于索拉非尼，OS分别为8.7个月和10.6个月（P=0.031）。而Kudo等[12]的研究结果表明，HAIC（顺铂+5-FU）加索拉非尼疗效对比索拉非尼，OS分别为11.8个月和11.5个月（P=0.955）。序贯HAIC（顺铂）联合索拉非尼对比索拉非尼的SCOOP-2研究同样也未能延长患者的生存时间，OS为10.0个月比15.2个月（P=0.78）[13]。尽管灌注顺铂为基础的HAIC联合索拉非尼的获益不尽相同，但亚组分析提示对于合并门静脉癌栓的肝癌患者疗效确切。HAIC（FOLFOX）联合索拉非尼证实了这一结论。一项Ⅲ期研究证实，HAIC（FOLFOX）联合索拉非尼治疗肝癌门静脉主干癌栓患者延长了OS，为13.37个月比7.13个月（P<0.01）[14]。Wang等[15]研究提示，联合组有更高的ORR（57.1%比4.0%，P<0.01）、更长的PFS（10.7个月比2.5个月，P<0.01）和OS（23.5个月比6.8个月，P<0.01）。基于上述研究，2021年JSH共识建议推荐HAIC和索拉非尼的联合应用，为血管侵犯患者提供生存益处[4]。

1.2 HAIC联合仑伐替尼

REFLECT研究证实，仑伐替尼在改善ORR和PFS方面优于索拉非尼[16]，且仑伐替尼和HAIC被日本指南推荐为晚期肝癌的标准治疗。为进一步提升缓解率和增加生存获益，肝癌专家开始探索HAIC联合仑伐替尼治疗效果。2020年ASCO会议报道了24例HAIC（FOLFOX）联合仑伐替尼治疗晚期肝癌的回顾性研究，结果显示ORR分别为58.3%（RECIST）和66.7%（mRECIST），DCR为79.2%，PFS为8.1个月，1年存活率为75%[17]。2021年ESMO会议公布了HAIC（顺铂）联合仑伐替尼（LEOPARD）研究结果，ORR为45.7%（RECISTv1.1）和64.7%（mRECIST），PFS和OS分别为6.3个月和17.2个月。3～4级主要不良事件为AST升高（34%）、低钠血症（25%）、白细胞减少（22%）、ALT升高（19%）和高血压（11%）[18]。HAIC联合仑伐替尼治疗晚期肝癌获得了较好的ORR，相比仑伐替尼单药提升近40%，但是缺少前瞻性随机对照试验，仍需探索其获益情况。

2 HAIC联合免疫检查点抑制剂

免疫治疗彻底变革了肝癌系统治疗格局，但客观缓解率不足20%。前期研究发现，局部介入治疗可以激活免疫系统，通过诱导局部炎症和释放新抗原提高PD-1（programmed death-1）抗体的疗效[19-21]。在一项前瞻性、非随机对照Ⅱ期研究中，评估了HAIC联合信迪利单抗对比HAIC治疗局部晚期、潜在可切除肝癌的疗效和安全性。联合组的CR和PR分别为9.5%（2/21）和33.3%（7/21），对照组分别为0和40%（P<0.01）[22]。另一项研究表明HAIC联合PD-1单抗治疗总体缓解率（83%比66%，P=0.006）、肝内缓解率（85%比74%，P=0.045）、PFS（10.0个月比5.6个月，P=0.006）和OS（18.0个月比14.6个月，P=0.018）均高于HAIC组[23]。肝癌HAIC联合免疫治疗尚处于探索阶段，有待进一步观察。另有2项HAIC联合免疫治疗的试验正在进行中，一项是HAIC与特瑞普利单抗（Ⅱ期，NCT04135690），另一项是HAIC与度伐利尤单抗（Ⅱ期，NCT04945720）。

3 HAIC联合免疫检查点抑制剂和分子靶向药物

免疫检查点抑制剂联合分子靶向药物治疗肝癌的ORR为20%～46%，PFS为4.6～9.7个月[4]。基于HAIC的联合免疫和靶向治疗可显著改善肝癌患者的ORR（40%～100%）和PFS（8.8～11.1个月），

ORR及PFS的提升为延长OS奠定基础[24-28]。Gu等[24]报道了HAIC联合特瑞普利单抗和阿帕替尼治疗晚期肝癌的疗效，ORR为100%（3例为CR，3例为PR），尽管纳入病例数较少，但初步展现了三联治疗的优异近期疗效。一项多中心回顾性研究比较了HAIC（FOLFOX）联合特瑞普利单抗及仑伐替尼（n=71）与仑伐替尼（n=86）治疗肝癌患者的疗效，结果显示联合治疗组的ORR（RECIST：59.2%比9.3%，P<0.01；mRECIST：67.6%比16.3%，P<0.01）、PFS（11.1个月比5.1个月，P<0.01）和OS（未达到与11个月，P<0.01）均优于单药组[27]。另一项回顾性研究显示，三联疗法的ORR、PFS和OS均优于PD-1单抗联合仑伐替尼组（ORR为40.0%比16.0%，P=0.038；PFS为8.8个月比5.4个月，P=0.0320；OS为15.9个月比8.6个月，P=0.0015）[28]。HAIC联合免疫和靶向治疗方案的3/4级治疗不良反应发生率为8.5%～20%，主要是与化疗相关的血液系统毒性，但耐受性较好。现有多项临床研究正在开展以评估HAIC联合免疫和靶向治疗效果和安全性（NCT05029973、NCT04947826、NCT04961918、NCT05003700）。

4　HAIC联合系统治疗在肝癌转化治疗的应用

目前我国肝癌手术切除率不足30%，对于不可切除肝癌可采用多种治疗方式以达到转化切除目的[29-31]。研究显示，HAIC在肝癌的降期和转化方面有独特优势[29]。一项研究报道，HAIC作为辅助治疗超出米兰标准的BCLC A/B期肝癌，pCR率为10.1%，ORR为63.6%，DCR为96.0%，3年生存率从46.3%提升到63.5%。FOHAIC-1研究中，有16例患者实现肿瘤降期，其中15例接受了根治性手术或消融，中位PFS和OS分别为20.8个月和16.4个月。HAIC与系统疗法的结合也展示了较高的ORR和手术转化率。信迪利单抗联合HAIC（FOLFOX）治疗晚期肝癌，17例行手术切除，手术率为65.4%（17/26）[22]。LTHAIC研究中，8例患者达到降期目的，其中1例行肝移植，4例行根治性手术切除，其中1例获得CR[25]。笔者团队目前正在开展HAIC联合免疫及靶向治疗在不可切除中晚期肝癌的临床研究。前期临床研究发现，联合治疗能迅速缩小肿瘤且持续控制肝内病灶，且对肝功能的影响甚微，为后续手术提供良好的肝功能储备。另外，不同于以往TACE联合治疗导致的癌周组织黏连、手术难度大、大肝癌栓塞不完全等劣势，HAIC治疗放弃了栓塞剂，产生的炎症反应少，降低了手术风险，是一种较理想的术前辅助治疗方法。

总之，HAIC联合系统治疗是有效且安全的。HAIC联合索拉非尼不能使肝癌患者在PFS、OS方面显著获益，但对于合并门静脉主干癌栓的患者应尽早联合治疗。HAIC联合仑伐替尼或免疫检查点抑制剂当前证据不足，临床应用价值需进一步探讨。HAIC联合分子靶向药物以及免疫检查点抑制剂展现了引人瞩目的疗效和安全性，但缺乏全球多中心的随机对照研究。另外，对于联合治疗方案的选择、药物剂量、续贯方案、潜在的获益群体以及与联合治疗相关的毒性等问题仍需深入探讨。

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