

肝动脉灌注化疗(HAIC)治疗肝细胞癌(HCC)的研究进展

许书榕^{1,2}(综述) 陈荣新^{1,2Δ}(审校)

(¹ 复旦大学附属中山医院肝内科 上海 200032; ² 复旦大学肝癌研究所 上海 200032)

【摘要】 肝动脉化疗栓塞、分子靶向治疗和免疫治疗是目前晚期肝细胞癌(hepatocellular carcinoma, HCC)的推荐治疗方法,但尚缺乏治疗无效或失败后的补救治疗。晚期 HCC 患者接受肝动脉灌注化疗(hepatic arterial infusion chemotherapy, HAIC)有生存获益,提示 HAIC 可能是各种肝癌治疗无效或失败后的一种补救治疗方法。尽管既往研究表明 HAIC 对晚期 HCC 治疗有效,但是缺少大样本随机对照临床试验的数据。为了使 HAIC 成为晚期 HCC 推荐治疗方法,须将 HAIC 与其他标准治疗方法进行比较;寻找对 HAIC 治疗有反应的预测指标,优化和统一 HAIC 治疗方案等。本综述旨在提供 HAIC 临床应用的研究进展。

【关键词】 肝细胞癌(HCC); 肝动脉; 经动脉灌注; 化疗

【中图分类号】 R735.7 **【文献标识码】** B **doi:** 10.3969/j.issn.1672-8467.2019.06.016

Research advances in the treatment of hepatic arterial infusion chemotherapy (HAIC) for hepatocellular carcinoma (HCC)

XU Shu-rong^{1,2}, CHEN Rong-xin^{1,2Δ}

(¹ Department of Hepatology, Zhongshan Hospital, Fudan University, Shanghai 200032, China;

² Liver Cancer Institute, Fudan University, Shanghai 200032, China)

【Abstract】 Hepatic arterial chemoembolization, molecular targeted therapy and immunotherapy are currently recommended treatments for advanced hepatocellular carcinoma (HCC). However, there is a lack of remedial treatment after these treatments are ineffective or failed. Some studies have found that hepatic artery infusion chemotherapy (HAIC) has a survival benefit in patients with advanced HCC, suggesting that HAIC may be a salvage treatment for the failure or ineffectiveness of various treatments. Although previous studies have shown that HAIC is effective in the treatment of advanced HCC, data from large randomized controlled clinical trials are missing. In order to make HAIC as a recommended treatment for advanced HCC, much more work needs to be done; HAIC to be compared with current standard treatments for advanced HCC; to delineate predictive indicators for efficacy of HAIC; to optimize and standardize HAIC treatment. This review aims to provide an introduction of the research progresses in clinical applications of HAIC treatment.

【Key words】 hepatocellular carcinoma (HCC); hepatic artery; infusion, intra-arterial; chemotherapy

* This work was supported by the National Natural Science Foundation of China (81272723) and the Supporting Project of Medical Guidance (traditional Chinese and Western Medicine) of Shanghai Science and Technology Commission (19411970400).

肝细胞癌(hepatocellular carcinoma, HCC)是全球第4位癌症死亡原因^[1], 25%~70%的患者诊断时已为晚期, 中位生存期仅为4.2~7.9个月^[2-3]。约75%的HCC发生在亚洲, 中国占世界负担的50%以上^[4]。肝癌发病率在未来10~20年内仍处于增加态势, 并将在2030年左右达到峰值^[5]。索拉非尼是延长晚期HCC患者生存时间的有效分子靶向药物^[6], 但是其局限性包括: 客观反应率低^[2]、生存获益有限^[3]、个体反应高度异质性^[7]、乙型肝炎病毒相关肝癌不敏感等^[8]。近年来, 其他分子靶向药和免疫检查点抑制剂被推荐用于晚期肝癌治疗。HCC总体5年生存率仍然小于12%^[9], 晚期HCC情况更不容乐观, 因此迫切需要新的治疗方法或替代治疗^[1,10-11]。

晚期 HCC 治疗选择 根据美国肝病研究协会(AASLD) HCC管理实践指南, 索拉非尼是用于肝功能代偿的晚期HCC患者一线治疗药物^[12-13]。两项大型国际多中心、随机对照临床试验SHARP和Oriental研究显示, 索拉非尼可延长晚期HCC患者生存期。SHARP研究报道, 索拉非尼和安慰剂组的患者中位生存期分别为10.7和7.9个月^[3], 1年生存率分别为44%和33%。除了各国指南推荐的索拉非尼之外, 其他分子靶向药物、免疫检查点抑制剂, 如仑伐替尼、瑞戈非尼、卡博替尼、雷莫卢单抗、PD1单抗Opdivo、PD1单抗Keytruda联合仑伐替尼、PD1单抗Atezolizumab联合贝伐单抗治疗晚期HCC取得了很大进展^[14-16]。小样本的仑伐替尼联合Keytruda治疗晚期HCC患者(含初治及索拉非尼耐药), 有效率在35%以上, 疾病控制率为100%。

虽然晚期HCC治疗已取得很多进展, 但是缺少这些治疗无效或者失败后的补救治疗方法。肝动脉灌注化疗(hepatic artery infusion chemotherapy, HAIC)对晚期HCC有治疗作用, 由于没有在大规模随机临床试验中进行验证, 美国AASLD和欧洲肝病学会(EASL)的HCC指南没有将其作为晚期HCC推荐治疗。美国国立综合癌症网络(NCCN)肝胆癌指南、亚太肝脏研究协会(APASL)肝癌指南中, 晚期HCC治疗计划不包括HAIC^[5,17-18]。然而, 日本HCC临床实践指南及一项HAIC治疗HCC的历史对照研究建议, 晚期HCC患者使用HAIC可改善患者的预后^[19]。

HAIC对比索拉非尼治疗 多中心、开放标记、

随机Ⅱ期临床试验用于评估顺铂方案的HAIC与索拉非尼联合治疗晚期HCC的效果, 结果显示: 接受联合治疗的患者生存明显优于单独使用索拉非尼的患者, 中位生存期(median survival time, MST)分别为10.6和8.7个月, 风险比(hazard ratio, HR)为0.60($P=0.031$)^[20-22]。Song等^[23]报道门静脉癌栓晚期HCC患者, 50例接受顺铂、5-FU和表柔比星方案的HAIC治疗, 60例接受索拉非尼治疗。HAIC治疗在MST(7.1个月 vs. 5.5个月, $P=0.011$)和至疾病进展时间(time to progress, TTP)(3.3个月 vs. 2.1个月)方面, 均优于索拉非尼治疗($P=0.034$)^[23]。Kudo等^[24]比较了索拉非尼联合低剂量顺铂和5-FU的HAIC治疗与单用索拉非尼治疗晚期HCC的临床效果(SILIUS研究), 索拉非尼加HAIC组与索拉非尼单药组的中位生存期相似[11.8(95%CI: 9.1~14.5)个月 vs. 11.5(95%CI: 8.2~14.8)个月, $P=0.955$]。索拉非尼加HAIC治疗组的3~4级不良事件发生率高于索拉非尼单药组。索拉非尼联合HAIC治疗与索拉非尼单药治疗的患者生存没有显著差异, 需要进一步研究^[24-25]。

HAIC治疗方案 HAIC在亚洲特别是日本得到广泛应用。HAIC治疗晚期HCC的应答率为7%~81%, MST为6~15.9个月^[26]。理论上HAIC比全身化疗对肝癌更有效, 因为肝动脉灌注抗癌药物可以直接向高血管性肝癌输送高剂量药物。肝内首过效应导致HAIC药物全身水平低于全身给药, 降低了药物的毒性作用和不良反应。然而, 没有证据显示HAIC与全身化疗或最佳支持治疗相比有生存优势。HAIC治疗方案包括单用或联合给药; 使用的药物包括5-FU、顺铂(cis-diamine dichloroplatinum, CDDP)、阿霉素、奥沙利铂、表柔比星、丝裂霉素C、抗肿瘤药净司他丁苯马聚合物(stimalamer zinostatin)、米铂(miriplatin)、FOLFOX、干扰素(interferon, IFN)等。目前, HAIC治疗最佳方案尚未统一。

FAIT方案 FAIT方案(IFN联合5-FU)的HAIC应答率为30%~40%^[27-32], MST为8.4~10.5个月^[27-28,31]。Obi等^[32]评估了FAIT治疗伴门静脉侵犯的HCC患者($n=116$)的有效性和安全性, 并与历史对照的患者($n=40$)进行比较, 其中FAIT治疗组19例(16%)患者完全缓解, 42例(36%)患者部分缓解, 不良反应仅有恶心和食欲不

振,12和24个月生存率分别为34%和18%,而历史对照组分别为15%和5%,提示FAIT显著提高伴门静脉侵犯晚期肝癌患者的生存率^[32]。在FAIT中,IFN作为5-FU的生化调节剂,增强其抗肿瘤作用。IFN直接抑制内皮细胞增殖,间接影响血管生成。FAIT方案不良反应小,治疗安全,对于血管侵犯的晚期HCC是一个值得考虑的治疗方案。

低剂量FP方案 低剂量FP方案(低剂量CDDP联合5-FU)的HAIC应答率在30%~40%^[33-36]。Nouso等^[37]报道,476例接受5-FU和顺铂HAIC的HCC患者与1466例未接受积极治疗患者进行比较,在调整已知风险因素后,HAIC生存获益明显(HR=0.48,95%CI:0.41~0.56, $P<0.0001$)。在倾向评分匹配分析中,接受HAIC治疗患者的MST比未接受积极治疗的患者更长(14.0个月 vs 5.2个月,HR=0.60,95%CI:0.49~0.73, $P<0.0001$)。肿瘤超过3个、Child-Pugh A或B患者接受HAIC治疗后MST比未治疗患者长(13.9个月 vs 3.7个月, $P<0.0001$)。门静脉癌栓、Child-Pugh A或B患者接受HAIC治疗后MST也明显长于未治疗的患者(7.9个月 vs 3.1个月, $P<0.0001$)。

单独使用CDDP 单独使用CDDP的HAIC治疗晚期HCC的应答率在20%~30%^[38-42],MST为5.0~11.2个月^[30,39-42]。对于早期HCC,HAIC也显示出一定的作用。Ishikawa等^[43]比较了早期HCC患者在根治性局部治疗前接受高浓度CDDP HAIC治疗与未治疗患者的疗效:非HAIC治疗组的1年、3年和5年生存率分别为77.4%、69.2%和55.3%,在HAIC组这些指标分别为97.4%、87.0%和84.4%。HAIC治疗组患者的生存时间显著延长,提示高浓度CDDP的HAIC治疗在根治性局部治疗前可改善早期HCC患者预后。CDDP通过与鸟嘌呤或腺嘌呤7位上的N结合,引起DNA链间或链内交联,导致DNA断裂,抑制DNA复制和转录,从而发挥抗癌作用。CDDP抗肿瘤作用有时间依赖性和浓度依赖性。

FOLFOX方案 FOLFOX方案(奥沙利铂+5-FU+亚叶酸钙)全身化疗对晚期HCC有效^[44]。He等^[45]对无法手术切除的HCC患者进行了一项前瞻性非随机II期研究,接受FOLFOX方案HAIC治疗组的患者,部分缓解率和疾病控制率均高于TACE治疗组(52.6% vs 9.8%, $P<0.001$;83.8%

vs. 52.5%, $P=0.004$)。HAIC治疗组和TACE组中位TTP分别为5.87和3.6个月($P=0.015$)。HAIC治疗后患者接受肝切除术数量也比TACE组多(10 vs. 3, $P=0.033$)。HAIC治疗组3~4级不良事件(adverse event, AE)和严重不良事件(serious adverse event, SAE)比例低于TACE组(3~4级AE:13次 vs. 27次, $P=0.007$;SAE:6次 vs. 15次, $P=0.044$)。Lyu等^[46]报道55例晚期HCC患者,接受FOLFOX方案HAIC治疗,总有效率达79.6%,明显优于之前的索拉非尼疗效(SHARP研究中索拉非尼有效率为43%)。另一回顾性研究中,180例晚期HCC患者接受FOLFOX方案HAIC治疗,232例接受索拉非尼治疗,两组患者MST分别为14.5和7.0个月($P<0.001$)^[47]。这些研究显示,FOLFOX方案的HAIC治疗局部晚期HCC具有优势,为患者带来生存获益,提高生活质量,且耐受性良好,不良反应较轻^[46-47]。

HAIC治疗的预后因素 Child-Pugh评分、甲胎蛋白(alpha fetoprotein, AFP)水平和治疗效果是接受HAIC治疗患者的重要预后因素^[48-49]。Miyaki等^[50]发现影像学评价结合AFP和脱- γ -羧基凝血酶原(des-gamma-carboxyprothrombin, DCP)变化能够提前预测HAIC疗效。早期影像学上的肿瘤也与患者生存相关,实体瘤疗效评价标准(Response Evaluation Criteria in Solid Tumors, RECIST)评价为部分缓解(partial response, PR)、疾病稳定(stable disease, SD)和疾病进展(progressive disease, PD),MST分别为20.6、11.4和5.0个月($P<0.0001$)。治疗前后AFP和DCP比值与患者MST也相关,AFP和DCP比值均 >1 的患者MST最低(6.55个月)。在临床实践中,首次HAIC治疗后通过影像学评价、肿瘤标志物变化可以区分对HAIC治疗有无响应。对HAIC治疗早期无应答者,治疗策略应做相应改变。Niizeki等^[51]报道血清血管内皮生长因子水平是晚期HCC患者接受低剂量FP方案HAIC治疗后疗效及患者生存重要预测因子。使用IFN- α 和5-FU的HAIC治疗患者,其预后与IFN- α 受体表达有关^[29],但需要HCC组织标本来评估这些参数。

炎症在各种癌症发生和进展中起关键作用^[52]。Tajiri等^[53]报道接受HAIC治疗患者的中性粒细胞与淋巴细胞比率(neutrophil to lymphocyte ratio, NLR)为4或更高与低应答率相关,而NLR低于4

则与治疗的应答率高、患者生存延长相关。另一项研究中,高 NLR 患者(临界值 2.87)与低 NLR 患者相比,HAIC 治疗后 MST 显著缩短(8.0 个月 *vs.* 20.7 个月, $P < 0.01$),治疗应答率较差(21.1% *vs.* 37.7%, $P < 0.01$),提示 NLR 水平与 HAIC 治疗的反应率相关性($P = 0.024$),NLR 是评估患者预后的独立指标^[54]。

结语 HAIC 对晚期 HCC 有肯定的治疗作用,可能是其他治疗无效或失败后的补救治疗选择之一。HAIC 治疗面临的问题:肝动脉置管技术、最佳治疗方案标准化;早期识别对 HAIC 治疗有响应患者;缺少大规模随机对照临床试验等。HAIC 将在治疗标准化、消融治疗、分子靶向治疗及免疫治疗(PD-L1 抗体)等联合使用方面得到进一步探索。

参 考 文 献

- [1] AKINYEMIJU T, ABERA S, AHMED M, *et al.* The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015[J]. *JAMA Oncol*, 2017, 3(12): 1683 - 1691.
- [2] CHENG AL, KANG YK, CHEN Z, *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial [J]. *Lancet Oncol*, 2009, 10(1): 25 - 34.
- [3] LLOVET JM, RICCI S, MAZZAFERRO V, *et al.* Sorafenib in advanced hepatocellular carcinoma [J]. *N Engl J Med*, 2008, 359(4): 378 - 390.
- [4] LAI CL, RATZIU V, YUEN MF, *et al.* Viral hepatitis B [J]. *Lancet*, 2003, 362(9401): 2089 - 2094.
- [5] OMATA M, CHENG AL, KOKUDO N, *et al.* Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update [J]. *Hepatol Int*, 2017, 11(4): 317 - 370.
- [6] BRUIX J, REIG M, SHERMAN M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma [J]. *Gastroenterology*, 2016, 150(4): 835 - 853.
- [7] CHEN J, JIN R, ZHAO J, *et al.* Potential molecular, cellular and microenvironmental mechanism of sorafenib resistance in hepatocellular carcinoma [J]. *Cancer Lett*, 2015, 367(1): 1 - 11.
- [8] JACKSON R, PSARELLI EE, BERHANE S, *et al.* Impact of viral status on survival in patients receiving sorafenib for advanced hepatocellular cancer: a meta-analysis of randomized phase III trials [J]. *J Clin Oncol*, 2017, 35(6): 622 - 628.
- [9] EL-SERAG HB. Hepatocellular carcinoma [J]. *N Engl J Med*, 2011, 365(12): 1118 - 1127.
- [10] PARSONS HM, CHU Q, KARLITZ JJ, *et al.* Adoption of sorafenib for the treatment of advanced-stage hepatocellular carcinoma in oncology practices in the united states [J]. *Liver Cancer*, 2017, 6(3): 216 - 226.
- [11] PARK JW, CHEN M, COLOMBO M, *et al.* Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study [J]. *Liver Int*, 2015, 35(9): 2155 - 2166.
- [12] BRUIX J, SHERMAN M. Management of hepatocellular carcinoma: an update [J]. *Hepatology*, 2011, 53(3): 1020 - 1022.
- [13] BRUIX J, GORES GJ, MAZZAFERRO V. Hepatocellular carcinoma: clinical frontiers and perspectives [J]. *Gut*, 2014, 63(5): 844 - 855.
- [14] DAWKINS J, WEBSTER RM. The hepatocellular carcinoma market [J]. *Nat Rev Drug Discov*, 2018.
- [15] BRUIX J, QIN S, MERLE P, *et al.* Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial [J]. *Lancet*, 2017, 389(10064): 56 - 66.
- [16] EL-KHOUEIRY AB, SANGRO B, YAU T, *et al.* Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial [J]. *Lancet*, 2017, 389(10088): 2492 - 2502.
- [17] EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma [J]. *J Hepatol*, 2018, 69(1): 182 - 236.
- [18] BENSON AR, D'ANGELICA MI, ABBOTT DE, *et al.* NCCN Guidelines Insights: Hepatobiliary Cancers, Version 1. 2017 [J]. *J Natl Compr Canc Netw*, 2017, 15(5): 563 - 573.
- [19] HATOOKA M, KAWAOKA T, AIKATA H, *et al.* Hepatic arterial infusion chemotherapy followed by sorafenib in patients with advanced hepatocellular carcinoma (HICS 55): an open label, non-comparative, phase II trial [J]. *BMC Cancer*, 2018, 18(1): 633.
- [20] IKEDA M, SHIMIZU S, SATO T, *et al.* Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial [J]. *Ann Oncol*, 2016, 27(11): 2090 - 2096.
- [21] FORNARO L, VIVALDI C, LORENZONI G, *et al.* Moving beyond sorafenib alone in advanced hepatocellular carcinoma: is hepatic arterial infusion chemotherapy the best option? [J]. *Ann Oncol*, 2017, 28(3): 667.
- [22] IKEDA M, SHIMIZU S, SATO T, *et al.* Reply to the Letter to the editor ' Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus Sorafenib for advanced hepatocellular carcinoma: randomized phase II trial' by Fornaro *et al* [J]. *Ann Oncol*, 2017, 28(4): 903 - 904.
- [23] SONG DS, SONG MJ, BAE SH, *et al.* A comparative

- study between sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis[J]. *J Gastroenterol*, 2015, 50(4):445-454.
- [24] KUDO M, UESHIMA K, YOKOSUKA O, *et al.* Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial[J]. *Lancet Gastroenterol Hepatol*, 2018, 3(6):424-432.
- [25] SAEKI I, YAMASAKI T, MAEDA M, *et al.* Treatment strategies for advanced hepatocellular carcinoma: Sorafenib vs hepatic arterial infusion chemotherapy[J]. *World J Hepatol*, 2018, 10(9):571-584.
- [26] OBI S, SATO S, KAWAI T. Current status of hepatic arterial infusion chemotherapy[J]. *Liver Cancer*, 2015, 4(3):188-199.
- [27] YAMASHITA T, ARAI K, SUNAGOZAKA H, *et al.* Randomized, phase II study comparing interferon combined with hepatic arterial infusion of fluorouracil plus cisplatin and fluorouracil alone in patients with advanced hepatocellular carcinoma[J]. *Oncology*, 2011, 81(5-6):281-290.
- [28] NAGANO H, WADA H, KOBAYASHI S, *et al.* Long-term outcome of combined interferon-alpha and 5-fluorouracil treatment for advanced hepatocellular carcinoma with major portal vein thrombosis [J]. *Oncology*, 2011, 80(1-2):63-69.
- [29] OTA H, NAGANO H, SAKON M, *et al.* Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil; role of type 1 interferon receptor expression[J]. *Br J Cancer*, 2005, 93(5):557-564.
- [30] IKEDA M, OKUSAKA T, FURUSE J, *et al.* A multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis[J]. *Cancer Chemother Pharmacol*, 2013, 72(2):463-470.
- [31] MONDEN M, SAKON M, SAKATA Y, *et al.* 5-fluorouracil arterial infusion + interferon therapy for highly advanced hepatocellular carcinoma; a multicenter, randomized, phase II study[J]. *Hepatol Res*, 2012, 42(2):150-165.
- [32] OBI S, YOSHIDA H, TOUNE R, *et al.* Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion[J]. *Cancer*, 2006, 106(9):1990-1997.
- [33] UESHIMA K, KUDO M, TANAKA M, *et al.* Phase I / II study of sorafenib in combination with hepatic arterial infusion chemotherapy using low-dose cisplatin and 5-fluorouracil[J]. *Liver Cancer*, 2015, 4(4):263-273.
- [34] NAKANO M, NIIZEKI T, NAGAMATSU H, *et al.* Clinical effects and safety of intra arterial infusion therapy of cisplatin suspension in lipiodol combined with 5-fluorouracil versus sorafenib, for advanced hepatocellular carcinoma with macroscopic vascular invasion without extra hepatic spread; a prospective cohort study[J]. *Mol Clin Oncol*, 2017, 7(6):1013-1020.
- [35] SAEKI I, YAMASAKI T, TANABE N, *et al.* A new therapeutic assessment score for advanced hepatocellular carcinoma patients receiving hepatic arterial infusion chemotherapy[J]. *PLoS One*, 2015, 10(5):e126649.
- [36] KAWAOKA T, AIKATA H, KOBAYASHI T, *et al.* Comparison of hepatic arterial infusion chemotherapy between 5-fluorouracil-based continuous infusion chemotherapy and low-dose cisplatin monotherapy for advanced hepatocellular carcinoma[J]. *Hepatol Res*, 2018, 48(13):1118-1130.
- [37] NOUSO K, MIYAHARA K, UCHIDA D, *et al.* Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan[J]. *Br J Cancer*, 2013, 109(7):1904-1907.
- [38] YOSHIKAWA M, ONO N, YODONO H, *et al.* Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma[J]. *Hepatol Res*, 2008, 38(5):474-483.
- [39] KONDO M, MORIMOTO M, NUMATA K, *et al.* Hepatic arterial infusion therapy with a fine powder formulation of cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis[J]. *Jpn J Clin Oncol*, 2011, 41(1):69-75.
- [40] IWASA S, IKEDA M, OKUSAKA T, *et al.* Transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization[J]. *Jpn J Clin Oncol*, 2011, 41(6):770-775.
- [41] KONDO M, MORIMOTO M, ISHII T, *et al.* Hepatic arterial infusion chemotherapy with cisplatin and sorafenib in hepatocellular carcinoma patients unresponsive to transarterial chemoembolization; a propensity score-based weighting[J]. *J Dig Dis*, 2015, 16(3):143-151.
- [42] KIM BK, PARK JY, CHOI HJ, *et al.* Long-term clinical outcomes of hepatic arterial infusion chemotherapy with cisplatin with or without 5-fluorouracil in locally advanced hepatocellular carcinoma[J]. *J Cancer Res Clin Oncol*, 2011, 137(4):659-667.
- [43] ISHIKAWA T, KUBOTA T, ABE S, *et al.* Hepatic arterial infusion chemotherapy with cisplatin before radical local treatment of early hepatocellular carcinoma (JIS score 0/1) improves survival[J]. *Ann Oncol*, 2014, 25(7):1379-1384.
- [44] QIN S, BAI Y, LIM H Y, *et al.* Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia[J]. *J Clin Oncol*, 2013, 31(28):3501-3508.

- 鼠I型糖尿病的影响[J]. 中国病原生物学杂志, 2013, 8(7): 586-588.
- [28] DUPONT CD, CHRISTIAN DA, HUNTER CA. Immune response and immunopathology during toxoplasmosis [J]. *Semin Immunopathol*, 2012, 34(6): 793-813.
- [29] ARIF S, LEETE P, NGUYEN V, *et al.* Blood and islet phenotypes indicate immunological heterogeneity in type 1 diabetes [J]. *Diabetes*, 2014, 63(11): 3835-3845.
- [30] KANKOVA S, FLEGR J, CALDA P. An elevated blood glucose level and increased incidence of gestational diabetes mellitus in pregnant women with latent toxoplasmosis [J/OL]. *Folia Parasitol (Praha)*, 2015, 62: 1-6 [2018-09-21]. <https://folia.paru.cas.cz/pdfs/fol/2015/01/56.pdf>.
- [31] SEMENYA AA, SULLIVAN JS, BARNWELL JW, *et al.* Schistosoma mansoni infection impairs antimalaria treatment and immune responses of rhesus macaques infected with mosquito-borne Plasmodium coatneyi [J]. *Infect Immun*, 2012, 80(11): 3821-3827.
- [32] ELIAS D, AKUFFO H, PAWLOWSKI A, *et al.* Schistosoma mansoni infection reduces the protective efficacy of BCG vaccination against virulent mycobacterium tuberculosis [J]. *Vaccine*, 2005, 23(11): 1326-1334.
- [33] BOTELHO M, OLIVEIRA P, GOMES J, *et al.* Tumourigenic effect of Schistosoma haematobium total antigen in mammalian cells [J]. *Int J Exp Pathol*, 2009, 90(4): 448-453.

(收稿日期: 2018-12-21; 编辑: 段佳)

(上接第 818 页)

- [45] HE MK, LE Y, LI Q J, *et al.* Hepatic artery infusion chemotherapy using mFOLFOX versus transarterial chemoembolization for massive unresectable hepatocellular carcinoma: a prospective non-randomized study [J]. *Chin J Cancer*, 2017, 36(1): 83.
- [46] LYU N, LIN Y, KONG Y, *et al.* FOXAI: a phase II trial evaluating the efficacy and safety of hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin for advanced hepatocellular carcinoma [J]. *Gut*, 2018, 67(2): 391-395.
- [47] LYU N, KONG Y, MU L, *et al.* Hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin vs. sorafenib for advanced hepatocellular carcinoma [J]. *J Hepatol*, 2018, 69(1): 60-69.
- [48] ANDO E, TANAKA M, YAMASHITA F, *et al.* Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases [J]. *Cancer*, 2002, 95(3): 588-595.
- [49] MIYAKI D, AIKATA H, HONDA Y, *et al.* Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma according to Child-Pugh classification [J]. *J Gastroenterol Hepatol*, 2012, 27(12): 1850-1857.
- [50] MIYAKI D, KAWAOKA T, AIKATA H, *et al.* Evaluation of early response to hepatic arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma using the combination of response evaluation criteria in solid tumors and tumor markers [J]. *J Gastroenterol Hepatol*, 2015, 30(4): 726-732.
- [51] NIIZEKI T, SUMIE S, TORIMURA T, *et al.* Serum vascular endothelial growth factor as a predictor of response and survival in patients with advanced hepatocellular carcinoma undergoing hepatic arterial infusion chemotherapy [J]. *J Gastroenterol*, 2012, 47(6): 686-695.
- [52] MANTOVANI A, ALLAVENA P, SICA A, *et al.* Cancer-related inflammation [J]. *Nature*, 2008, 454(7203): 436-444.
- [53] TAJIRI K, KAWAI K, MINEMURA M, *et al.* Neutrophil/lymphocyte ratio as a prognostic indicator of hepatic arterial infusion chemotherapy with arterial cisplatin plus continuous 5-fluorouracil [J]. *Hepatol Res*, 2015, 45(7): 755-763.
- [54] TERASHIMA T, YAMASHITA T, IIDA N, *et al.* Blood neutrophil to lymphocyte ratio as a predictor in patients with advanced hepatocellular carcinoma treated with hepatic arterial infusion chemotherapy [J]. *Hepatol Res*, 2015, 45(9): 949-959.

(收稿日期: 2018-12-17; 编辑: 段佳)