指南(共识)解读

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《美国临床肿瘤学会晚期肝细胞癌系统治疗指南更新》解读

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【摘要】 2024-03-19,美国临床肿瘤学会(ASCO)发布了晚期肝细胞癌(HCC)系统治疗指南更新,此次更新基于2020年ASCO晚期HCC系统治疗指南的8项Ⅲ期随机对照试验(RCT),并整合了近年最新的10项RCT研究数据,建议将阿替利珠单抗+贝伐珠单抗或度伐利尤单抗+替西木单抗作为肝功能Child-Pugh A级、美国东部肿瘤协作组体力活动状态评分0~1分的晚期HCC病人的首选一线治疗方案,同时也解答了晚期HCC不同一线方案治疗后的二线及后线治疗的选择。

【关键词】 晚期肝细胞癌;美国临床肿瘤学会;系统治疗
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Interpretation on systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update

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Abstract On March 19, 2024, the American Society of Clinical Oncology (ASCO) released an update to the guidelines for the systemic treatment of advanced hepatocellular carcinoma (HCC). This update, based on eight phase Ⅲ randomized controlled trials (RCTs) from the 2020 ASCO guidelines, integrated ten latest RCT data in recent years and recommended atezolizumab plus bevacizumab or durvalumab plus tremelimumab as the preferred first-line treatment for advanced HCC patients with Child-Pugh A status and ECOG PS 0-1. It also addressed the selection of second-line and subsequent-line treatments for advanced HCC patients.

Keywords advanced hepatocellular carcinoma; the American Society of Clinical Oncology; systemic therapy

早期肝细胞癌(hepatocellular carcinoma,HCC)的治疗方法选择较多,包括肝切除术、肿瘤消融和肝移植术等,局部晚期HCC也可通过肝动脉化疗栓塞(transarterial therapies chemoembolization,TACE)、肝动脉灌注化疗(hepatic arterial infusion chemotherapy,HAIC)、外放射治疗、联合肝脏分隔和门静脉结扎二步肝切除术(associating liver partition and portal vein ligation for staged hepatectomy,ALPPS)等治疗方法来改善预后[1]。而对于晚期HCC病人,直至2008年酪氨酸激酶抑制剂(tyrosine kinase inhibitor,TKI)索拉非尼应用于临床,其生存才有所改善[2]。随后,几种新型免疫和靶向药物在晚期HCC一线和二线系统治疗中显示出有效性,并被纳入2020年美国临床肿瘤学会(American Society of Clinical Oncology,ASCO)晚期HCC系统治疗指南(简称ASCO指南),以帮助临床医生做出治疗决策[3-5]。近年来,随着越来越多的随机对照试验(RCT)结果发布,晚期HCC系统治疗药物的选择也日益增多。为了更好地指导临床实践,ASCO对晚期HCC系统治疗指南进行了更新,并于2024-03-19发表于*Journal of Clinical Oncology*(JCO)[6]。

1 指南更新的证据基础

ASCO指南更新工作是由包括了1例病人代表和1名具有医学研究方法学专业知识的ASCO指南工作人员的多学科专家小组负责。指南更新依次经过专家小组制定、公开评论建议和JCO编辑审阅,最终经由ASCO循证医学委员会审阅和批准后发表。

证据来源于2007-01-01至2023-10-05的PubMed数据库中针对晚期HCC的Ⅲ期RCT研究,研究对象为不能手术切除的晚期HCC病人,包括具有肝内多发和(或)浸润性病灶、广泛脉管浸润或肝外扩散等特征,且经评估后不适合手术或消融等治疗的HCC。同时排除以下文献:(1)在2年内未在同行评审的期刊上发表的会议摘要。(2)社论、评论、信件、新闻文章、病案报告和叙述性评论。(3)发表在非英文期刊的文章。

最终纳入文献为:(1)基于2020年ASCO指南的8项Ⅲ期RCT研究数据[3,7-13],并整合了其中2项(CheckMate459、IMbrave150)的研究进展[14-15]。(2)10项最新的RCT研究证据,包括7项一线系统治疗的RCT研究[16-22],2项二线系统治疗的研究RCT[23-24],以及1项初始未接受治疗或初始复发

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的RCT研究[25]。纳入文献中有7项我国原研药物或由我国肝胆胰外科专家牵头实施的RCT研究，具有重要的临床参考价值，也为全球晚期HCC病人系统治疗的进展做出了贡献[16-17,20-21,23-25]。

2　指南更新回答的主要问题、建议要点及点评

首先，ASCO指南更新回答了晚期HCC病人首选的一线系统治疗方案的问题。指南建议将阿替利珠单抗+贝伐珠单抗或度伐利尤单抗+替西木单抗作为肝功能和营养状态良好［肝功能Child-Pugh A级、美国东部肿瘤协作组（ECOG）体力活动状态评分（PS）0~1分］的晚期HCC病人的一线治疗方案，但须充分考虑贝伐珠单抗相关的出血和血栓形成的风险以及自身免疫性疾病。若经评估后仍存在明显的治疗禁忌证，可将索拉非尼、仑伐替尼或度伐利尤单抗作为替代的首选。

其次，ASCO指南更新还解答了晚期HCC病人二线或后线治疗的首选方案：（1）应用阿替利珠单抗（atezolizumab）+贝伐珠单抗（bevacizumab）一线治疗进展后，推荐使用索拉非尼（sorafenib）、仑伐替尼（lenvatinib）或卡博替尼（cabozantinib）等TKI类药物或雷莫西尤单抗［甲胎蛋白（AFP）≥400 μg/L］作为二线治疗首选，同时也将纳武利尤单抗（nivolumab）+伊匹木单抗（ipilimumab）或度伐利尤单抗（durvalumab）+替西木单抗（tremelimumab）纳入可选方案。（2）当使用度伐利尤单抗+替西木单抗一线治疗进展后，同样推荐TKI类药物作为二线治疗首选，同时阿替利珠单抗+贝伐珠单抗也可供选择。（3）当病人使用索拉非尼或仑伐替尼作为一线治疗时，专家组推荐使用另一种TKI类药物（卡博替尼或瑞戈非尼）、雷莫西尤单抗（AFP≥400 μg/L）、纳武利尤单抗+伊匹木单抗或度伐利尤单抗作为二线治疗首选，帕博利珠单抗（pembrolizumab）或纳武利尤单抗也可供参考。

在三线及后线治疗方面，ASCO指南建议在病人肝功能和营养状态（肝功能Child-Pugh A级、ECOG PS 0~1分）适合的情况下，可以考虑不同机制的上述一线或二线药物。

此外，ASCO指南更新还对晚期HCC系统治疗的其他关注点做了点评和分析。探讨篇幅最多的是肝功能Child-Pugh B或C级的晚期HCC病人系统治疗选择问题。其分析了多个以肝功能Child-Pugh B或C级病人为研究对象的RCT研究，发现上述推荐药物仍能使此类病人获益，但存在因不良反应而中止治疗的问题，且总体生存期短于肝功能Child-Pugh A级HCC病人。因此，ASCO指南建议在充分考虑基础肝功能变化、出血风险、是否存在门静脉高压、肿瘤肝内负荷、肿瘤肝外扩散和主要脉管浸润的情况下，谨慎使用上述推荐方案。

最后，ASCO指南更新还给出了晚期HCC系统治疗的未来导向：（1）利用特异性HCC生物标记物更精准地协助系统治疗方案决策。（2）二线及后续治疗方案的使用顺序及选择问题。（3）局部治疗与全身系统治疗联合使用的适用人群及具体方案的选择等。

总之，ASCO指南更新详细解答了晚期HCC病人在一、二线和后线系统治疗中药物选择的问题；针对不同的药物组合和使用顺序，也进行了明确的阐述；同时，还根据证据等级对推荐药物进行了区分。

3　ASCO指南与亚洲及我国相关指南的相同点和不同点

ASCO指南更新与《亚太肝病研究学会（APASL）肝细胞癌全身治疗临床实践指南》（简称APASL指南）和我国《原发性肝癌诊疗指南（2024版）》[26]（简称我国指南）有着较多的相同之处。首先，在晚期HCC一线系统治疗方面，基于IMbrave150的研究进展，阿替利珠单抗+贝伐珠单抗方案均获得了上述指南的首选推荐，且均提出须警惕和排除贝伐珠单抗带来的出血风险[27]；基于TKI类药物的抗肿瘤作用，各指南均推荐可用于晚期HCC的一线治疗，特别是对于存在出血风险或自身免疫病等免疫治疗相对禁忌证的病人。在晚期HCC二线治疗方面，各指南均强调瑞戈非尼、卡博替尼等TKI类药物的重要作用，可用于双免联合、免疫治疗联合抗血管生成药物或其他TKI类药物的二线治疗，同时也可应用帕博利珠单抗、雷莫西尤单抗（AFP≥400 μg/L）等单药免疫治疗。对于肝功能和营养状态良好的晚期HCC（肝功能Child-Pugh A级、ECOG-PS 0~1分）三线及后线治疗，各指南均提及可考虑应用与先前接受的不同作用机制的药物，但对于肝功能Child-Pugh B或C级病人用药应谨慎。

然而，由于不同地区HCC人群具有特定的疾病概况、发病原因和发展特点，ASCO与APASL指南和我国指南在治疗方式及药物选择上存在一定的差异。（1）以中国或亚洲人群为主体的RCT研究应用的免疫检查点抑制剂或TKI类药物未被ASCO纳入指南更新范畴，包括卡瑞利珠单抗、替雷利珠单抗、信迪利单抗、阿帕替尼及多纳非尼等部分我国原研药物。ASCO指南认为，HCC的病因、发展及转归在亚洲人群和西方人群之间存在明显差异，甚至不同亚洲国家或地区人群间也存在差异。我国HCC主要风险因素是乙型肝炎病毒（HBV），其他风险包括水污染、食品中的黄曲霉毒素以及过度饮酒；而在西方，主要风险因素是丙型肝炎病毒（HCV）和脂肪肝。我国HCC病人被诊断时往往年龄较轻，并且肿瘤负担更重、疾病更晚期，这可能导致预后较差，以及在综合治疗后较短的总体生存追踪随访时间。因此，此类药物对西方人群的获益有待进一步证实。（2）APASL指南和我国指南均更强调TACE等局部治疗及其联合系统治疗的重要性，这可能与亚洲病人群体肝内肿瘤负荷更重有关。EMERALD-1、LAUNCH等研究的成功再次证实了局部治疗联合全身靶免治疗的有效性，深刻地改变了中晚期肝癌局部治疗的格局[25,28]。（3）我国指南更推荐TKI类小分子靶向药物用于晚期HCC的系统治疗，除了推荐一线使用单药TKI外，CARES-310研究结果显示，TKI

联合程序性死亡受体1(PD-1)抑制剂的靶免组合(卡瑞利珠单抗+阿帕替尼)对比索拉非尼,在晚期HCC病人总生存期和无进展生存期上均有明显的改善,这一研究结论也纳入APASL指南[16]。目前,仍有多种靶免组合药物的研究正在进行,部分研究的Ⅱ期临床试验也取得了令人振奋的效果。

总体上,各指南求同存异,更加重视所在地区人群的获益情况,也充分考虑了不同地区HCC的病因和发展特点的差异。靶向联合免疫、双免联合、局部治疗联合系统治疗等多种治疗方案在有效性和耐受性方面普遍优于单药方案,越来越多联合方案的Ⅲ期临床试验正在进行,未来晚期HCC的系统治疗会有更多的选择,越来越多的晚期HCC病人也将从中获益。

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