直接抗病毒药物与肝细胞癌临床研究新进展

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摘要：丙型肝炎病毒（hepatitis C virus，HCV）感染是肝细胞癌（hepatocellular carcinoma，HCC）发生的重要原因之一。在过去的几十年中，基于干扰素的抗病毒治疗已被广泛接受。干扰素可通过实现持续病毒学应答（sustained virological response，SVR）而降低HCV相关肝硬化患者HCC的发生率及复发率，然而较低的持续病毒学应答率则限制了其进一步应用。近年来，随着直接抗病毒药物（direct antiviral agent，DAA）的应用，治疗方案已经发生了改变，DAA治疗可将HCV治疗的SVR率提高至95%以上。但基于DAA的无干扰素方案对HCC发生率及复发率的影响却仍存在争议。最初有研究报道了DAA治疗后的HCC高发生率和高复发率，而更近的研究则提供了大量证据对此进行驳斥。然而在获得更多中长期数据前，关于DAA治疗对于HCC发生率的影响尚无定论。本文现对DAA与HCC临床研究新进展进行综述。

关键词：肝炎病毒，丙型；肝细胞癌；直接抗病毒药物；持续病毒学应答；发生；复发

Clinical research on direct antiviral drugs and hepatocellular carcinoma

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Abstract: Hepatitis C virus (HCV) infection is one of the major causes of hepatocellular carcinoma (HCC). In recent decades, interferon (IFN) based regimens has been accepted by the public. This kind of anti-HCV therapy will decrease the occurrence and recurrence risks of HCV related HCC by achieving sustained virological response (SVR). However, the low SVR rate limits its extension. In the last couple of years, this situation has been changed by the introduction of direct antiviral agent (DAA). These drugs increase the SVR rate to higher than 95%. However, the effect of DAA-based interferon-free regimens on incidence and recurrence rate of HCC remains controversial. Some initial reports were in favor of an increased risk of HCC occurrence and recurrence after DAA therapies. Contrarily, recent reports provided plenty of evidence against it. The impact of DAA therapy on HCC risk will be inconclusive until more long-term and intermediate data become available. The clinical research on DAA and HCC were reviewed in this paper.

Key words: Hepatitis C virus; Hepatocellular carcinoma; Direct antiviral agent; Sustained virological response; Occurrence; Recurrence

1 丙型肝炎病毒感染概况

丙型肝炎病毒（hepatitis C virus，HCV）感染是慢性肝脏疾病的重要原因之一，现全球约有1.8亿HCV感染者，其中约7100万为慢性感染者[1]。HCV感染是威胁人类生命健康的重大卫生问题之一，也是导致肝细胞癌（hepatocellular carcinoma，HCC）的主要原因[1]。如何对患者进行安全有效的治疗是目前面临的最重要问题。在过去的几十年中，医务工作者一直致力于降低丙型肝炎发病率，减少包括HCC在内的HCV相关并发症。清除HCV、获得持续病毒应答（sustained virological response，SVR）是治疗HCV感染的目标。目前，以聚乙二醇化干扰素（pegylated interferon，PegIFN）联合利巴韦林（ribavirin，RBV）方案（PR方案）为基石的早期治疗被认为是抗HCV治疗的有效手段，且约50%患者可清除病毒或获得SVR[2]，大幅降低了HCC的发病率[3]。但PR方案应用范围窄、不良反应多、治愈率相对较低，限制了其进一步推广应用[4]。近年来，随着直接抗病毒药物（direct antiviral agent，

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DAA）的诞生，现有丙型肝炎的治疗局面发生了较大改变。DAA几乎可安全应用于所有人群，包括早期肝病及晚期肝病患者，且约95%患者可获得SVR[5]。但事实上，DAA治疗仍处于初期阶段，尚缺乏中期和远期观察数据。一些报道也提出DAA治疗可能导致更高的HCC发生率和复发率，因此需充分考虑DAA治疗过程中潜在的不良事件，进行有效的风险-效益分析，尤其针对肝硬化及肝癌患者。本研究对有关DAA治疗后新发及复发HCC情况进行综述，以提供更准确和合理的解释。

2 DAA 与 HCC

在HCV相关肝硬化人群中，HCC的年风险发生率为2%～8%[6]。对于有HCC病史的患者，即使已接受了肝脏切除等治疗性干预，5年复发率仍可达70%[7]。一项关于SVR的荟萃分析表明，SVR在阻止肝功能恶化、降低HCV相关HCC的发生风险以及提高总体生存率等方面具有重要作用，但即使已清除HCV，获得了SVR，仍不能消除HCC发生的风险，这种风险将会持续存在[8]。现有研究表明，绝大多数丙型肝炎患者均可通过DAA治疗达到SVR[5]，我们也期待DAA治疗能大幅度降低丙型肝炎肝硬化患者进展为肝癌的概率及肝癌患者复发的概率。但目前针对这一问题仍存在争议。

意大利的一项回顾性队列研究提出，DAA治疗可能会增加HCV相关肿瘤的发生率，研究者对接受DAA治疗的肝硬化患者进行24周随访后发现，HCC发生率达3.16%（9/285）[9]。同年，Cardoso等[10]也报道了DAA治疗后HCC的高发病率，其评估了240例接受无干扰素（interferon，IFN）治疗的肝硬化患者，排除了既往肝脏肿瘤病史及影像学显示“非特征性结节”等因素，最终纳入54例患者进行随访观察。所有患者均已接受为期24周的索非布韦联合雷迪帕韦治疗。在1年的随访期中，所有患者均达到SVR，其中4例患者（7.4%）发展为肝癌，远高于既往报道中接受IFN治疗患者的发病率（1.2%～1.4%）[10,11]。随后，Kozbial等[12]报道了6.6%的初发肿瘤发生率。Nakao等[13]研究中，DAA治疗后患者HCC的发生率远高于预期，1年和2年累积发生率分别达到1.75%和7%。

不仅如此，一些关于DAA治疗与复发性肝癌的研究结果也出乎人们预料。Reig等[14]首先提出，接受DAA治疗后肝癌患者的肿瘤复发率大幅提高。该研究纳入58例既往接受治疗的HCC患者，治疗包括根治性手术切除及微创治疗，如肝动脉化疗栓塞（transcatheter arterial chemoembolization，TACE）或射频消融（radiofrequency ablation，RFA），根据欧洲肝脏研究学会（European Association for the Study of the Liver，EASL）标准判定肿瘤完全坏死或无残留，影像学检查未提示肿瘤征象。在接受DAA治疗后的随访过程中（中位随访时间为5.7个月），16例（27.6%）患者肿瘤复发，其中2例在开始DAA治疗后的2周内即检测到复发肿瘤。更进一步的研究表明，此类复发肿瘤进展速度更快，侵袭性更强[15,16]。Conti等[9]的队列研究表明，肝癌复发率也达到了28.81%（17/59）（患者既往接受过肝脏肿瘤切除或局部消融等治疗，在研究开始前经电子计算机断层扫描或磁共振成像检查未发现复发征象）。EL Kassas等[17]的回顾性研究也表明，应用DAA后，肝癌复发率增加了3.82%。Yang等[18]的一项针对肝移植患者应用DAA治疗的小样本试验中，共纳入112例丙型肝炎相关肝癌患者，其中81例成功接受肝移植治疗，18例（22.22%）肝移植前接受过抗病毒治疗，结果表明移植前接受过口服DAA药物治疗患者的肝癌复发率更高（27.8% *vs* 9.5%）。

关于无干扰素的抗病毒治疗方案导致HCC发生率升高的原因目前尚无定论。一种推测是DAA使HCV病毒载量迅速下降引起机体免疫监视失调[8,19]，Ⅱ型和Ⅲ型IFN及其受体以及IFN刺激基因表达下调，缺乏IFN活化则可能导致肿瘤细胞生长。IFN可通过影响肿瘤调节血管的生成，调节免疫细胞的活性，从而发挥其抗肿瘤细胞增殖作用，而DAA并不具备以上两种作用[20]。另一种推测是在慢性HCV感染中，持续的抗原刺激有助于病毒特异性$CD8^+$ T细胞衰竭，激活肝脏中宿主介导的炎症，改变先天免疫细胞群，如黏膜相关恒定T细胞（mucosal-associated invariant T cell，MAIT细胞）和自然杀伤细胞（natural killer cell，NK细胞）。DAA迅速清除HCV后，机体免疫细胞群数量及种类发生改变，肝脏中缺乏持续的IFN刺激也可能对肝内免疫反应产生显著影响，使免疫反应在一定时间内处于不稳定状态，从而导致或加速HCC的发生[21,22]。Debes等[23]研究表明，接受DAA治疗后出现肝脏肿瘤的患者，其免疫介质的血清学表达水平显著升高。但目前相关理论仍有待进一步验证。

以上研究结果引起了极大关注。Torres等[24]认为，Reig等[14]的研究存在缺陷：首先，肝癌患者入组前接受的治疗种类过多（包括手术切除、RFA及TACE等）；其次，患者开始DAA治疗时与最后一次影像学检查所间隔的中位时间为1.7个月，间隔时间过长，DDA治疗开始2周内即检测到肿瘤复发，

不能排除在观察开始前患者就已经存在了未能检测到的肿瘤复发；第三，肝癌治疗后4个月内即评定治疗效果为完全缓解，时间相对较短，此外，作者也未描述这些肝癌患者既往肿瘤情况及具体治疗方案，治疗失败导致复发的因素也未考虑到；而且随访时间过短，仅5.7个月。以上因素导致此研究结果缺乏可重复性。Zeng等[25]参考Reig等[14]和Kozbial等[12]的研究设计相似的试验，随访追踪（中位随访时间为15个月）接受过DAA治疗的31例患者，随访期间未记录到任何肿瘤病例。同时，Kanwal等[26]认为，由于DAA治疗的应用范围更广，试验纳入的患者本身具有更多的HCC危险因素，如高龄、严重肝硬化及酒精滥用等，也一定程度上提高了HCC的发病率。

近两年来的更多研究表明，DAA是否会提高HCC发生率的问题仍需进一步探索。西班牙一项目前最大的真实世界研究中，近4000例接受DAA治疗的患者在18个月的随访观察期内HCC发生率仅为0.93%[27]。Calvaruso等[28]对DAA治疗早期丙型肝炎肝硬化研究共纳入2249例患者（Child-Pugh A级占90.5%，Child-Pugh B级占9.5%），其中78例患者在14个月随访期结束后进展为HCC（3.4%），但所有肿瘤并未显示出更高的侵袭性。Zavaglia等[29]也观察到DAA应用后的低肿瘤复发率（3.1%），同时作者提到，肿瘤完全根除与开始DAA治疗的时间间隔可能是导致各研究结果不同的重要原因之一。ANRS肝细胞癌合作研究组的一项前瞻性研究中共包含了3个不同队列，纳入超过6000例患者，同样得出DAA治疗不会增加HCC发生风险的结论[30]。不仅如此，对于成功接受过早期肝癌治疗的患者，DAA治疗可显著降低肿瘤复发率[31]。Cheung等[32]的前瞻性研究也表明，无任何证据可证明DAA治疗会增加肿瘤风险。其对接受DAA治疗的肝硬化失代偿期的患者进行随访观察，前6个月肝癌发生率为4%（17/406），第6～15个月肝癌发生率为2%（10/406），回顾对照6个月未接受DAA治疗的患者，HCC发生率为4%（11/261），组间无统计学差异。此外，对于在DAA治疗前3个月内即出现HCC的情况，作者认为并不能除外在抗病毒药物应用前患者就已经出现了无法检测到的肿瘤[32]，这与Torres等[24]的观点一致。Mettke等[33]的队列研究中，DAA治疗组和对照组HCC发生率分别为2.90/100人年和4.48/100人年，差异无统计学意义。

基于IFN的抗病毒治疗已被证明能够获得SVR，是通过获得SVR降低包括HCC在内的肝脏相关并发症发生风险的重要手段[8,28,34-37]。Mizuki等[38]比较了接受DAA治疗与IFN治疗患者的肿瘤复发率，结果表明1年及2年复发率均无显著差异。Tatsuya等[39]对RFA治疗后的肝癌患者的研究也得到相似结论。一项德国的队列研究表明，相比于IFN，DAA治疗并未增加初发肿瘤的几率（DAA：25/819 *vs* IFN：19/351）[40]。另一项德国的研究则认为DAA治疗可能会降低远期肿瘤发生率，DAA治疗组在1.5年后便未监测到肿瘤事件[33]。Karola等[41]研究纳入51例手术后的肝癌患者，术后应用DAA组肝癌复发时间在265 d（94～698 d）内，未应用DAA组肝癌复发时间在532 d（118～1360 d），其认为对于接受过手术治疗的晚期肝癌患者，DAA治疗虽不会增加肿瘤复发率，但可能会加速复发过程。但作者也认为此项研究的样本量过小，为进一步明确结论则需更多大样本的长期随访数据。

3 总结

通过对现有的DAA治疗后HCC发生风险数据的总结，包括最初提出DAA增加肿瘤风险的研究以及众多持反对意见的研究，可认为DAA并不会增加短期内肿瘤发生风险，但肝脏肿瘤风险依旧存在，无论既往有无肝癌病史，患者接受DAA治疗后都需接受长期密切随访，监测生物化学指标、影像学变化及血清生物标志物，尤其是对于具有肥胖、代谢综合征、人类免疫缺陷病毒感染、酒精滥用及既往抗病毒治疗失败等高危因素的患者[26,33,42-44]，监控应更严密。考虑到安全性问题，建议HCC患者最少在HCC治疗完全缓解的12个月后再接受DAA治疗，并应制定更密切的随访计划，而对于晚期肝硬化、抗病毒失败、有肿瘤复发史及高甲胎蛋白水平等复发风险高的患者[8,39,45-50]，DAA选择也应更加谨慎。由于无干扰素治疗方案的中期和长期数据相对空白，许多问题尚未解决，如DAA治疗的最佳时机、DAA治疗是否会改变复发肿瘤的表型、如何应对DAA治疗后的复发性肿瘤及如何评价DAA疗效等，因此需更多的前瞻性、大样本、随机对照试验进一步验证。

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