·专 论 Special comment·

经导管动脉化疗栓塞术抵抗研究进展

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【摘要】 经导管动脉化疗栓塞术(TACE)是巴塞罗那临床肝癌(BCLC)分期 B 期肝细胞肝癌(HCC)患者推荐治疗方案,已广泛应用于临床。但越来越多文献报道表明,TACE 作为一种姑息性治疗方案存在缺陷,如多次 TACE 治疗后肝癌病灶控制不佳,因此有学者提出“TACE 抵抗”观点。本文就 TACE 抵抗概念及其治疗进展作一论述。

【关键词】 肝细胞肝癌；经导管动脉化疗栓塞术；抵抗

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Transarterial chemoembolization refractory: current research progress *YU Chenxi, TENG Gaojun. Medical College, Southeast University, Nanjing, Jiangsu Province 210009, China*

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【**Abstract**】 Transarterial chemoembolization (TACE) is a standard treatment for Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma (HCC), and TACE has already been widely accepted in clinical practice. Recently, more and more researches have indicated that TACE, as a palliative therapeutic regimen, carries certain defects, e.g. after several times of TACE treatment the HCC lesions become poorly-controlled. Therefore, some scholars put forward the concept of “TACE refractory”. This paper aims to make a further discussion on the concept of TACE refractory and its treatment.(J Intervent Radiol, 2017, 26: 1063-1067)

【**Key words**】 hepatocellular carcinoma; transarterial chemoembolization; refractory

肝细胞肝癌(HCC)全球发病率位列肿瘤疾病第 5 位,肿瘤相关致死疾病第 2 位[1]。东亚、非洲撒哈拉以南地区及拉美尼西亚等发展中国家和地区高发，占全部病例 85%[2]，而中国约占全部病例 50%[1,3-4],是国内第 3 高发恶性肿瘤[5-6]。HCC 起病隐匿，超过 50%患者确诊时已处于中晚期状态,根治性切除率低,预后较差。文献报道 HCC 患者未经治疗的 1 年生存率仅为 17.5%[7]。HCC 评估系统包括 Okuda 分期[8]、意大利肝癌项目(CLIP)评分[9]、香港中文大学预后指数(CUPI)[10]、国际 HCC 协作研究组简化分级模型[11]及巴塞罗那临床肝癌(BCLC)分期[12]等,但目前临床和基础研究仍以 BCLC 分期为主要依据。

经导管动脉化疗栓塞术(TACE)[13-14]作为中期肝癌(BCLC B 期)标准化治疗方案[15-16],其原理为肝癌血供 90%以上来自肝动脉,门静脉主要为肿瘤引流静脉，仅参与肿瘤周边部位及包膜等处少量血供,而正常肝组织 70%～75%由门静脉供血,仅25%～30%源于肝动脉[17-18]。因此,经肝动脉注入化疗栓塞剂可有效阻断肿瘤血供、促使肿瘤组织坏死,同时实现化疗药物在肿瘤周围沉积,起到局部化疗作用[19-21],且优势在于降低肝脏损伤前提下对病灶进行有效治疗。多项研究表明 TACE 通过对病灶局部化疗、阻断肿瘤血供、致使肿瘤坏死,实现减少肿瘤生长和延长生存期效果[22-26]。但作为一种姑息疗法,TACE 也存在一些问题，最为突出的是肿瘤局部高复发率。多项随机对照研究表明，患者接受 TACE 治疗后持续 3～6 个月有效率仅为 28%～35%,初次 TACE 治疗后效果不佳患者与支持治疗患者相比未获明显生存获益[25]，原因可能是肿瘤病灶双重血供、病灶供血血管变异、反复栓塞导致病灶供血血管闭塞的缘故[27]。有实验表明 TACE 术后仅 10%～20%肿瘤组织呈完全性坏死，相当一部分肿瘤呈不

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完全坏死状态[28-30],原因可能与下列因素有关[31-33]:①肿瘤组织双重供血,肿瘤内中心区供血主要来自肝动脉,边缘区供血主要来自门静脉,单纯 TACE术后瘤内中心区病灶供血阻断而出现缺血性坏死,但对病灶边缘区供血影响较小,故残留癌细胞可导致复发;②沉积于肿瘤内碘油受血流冲刷及肝脏 Kupffer 细胞吞噬作用,可被癌细胞代谢并完全清除,对疗效影响较大;③TACE 术后肿瘤组织处于缺血缺氧状态,刺激血管再生,在病灶周围形成侧支或使病灶供血动脉再通。肿瘤不完全坏死导致肿瘤复发,影响 TACE 远期疗效。肿瘤肝内外转移也是导致TACE 术后患者预后不佳的因素[34-35]。有研究表明 TACE 术后缺血缺氧状态及化疗药物作用均可上调酪氨酸激酶受体家族成员 c-Met 表达[36],其配体为肝细胞生长因子(HGF)。HGF/c-Met 通路可控制肿瘤细胞浸润和转移,c-Met 高表达常伴随抗肿瘤治疗抵抗与肿瘤转移。

1 TACE 抵抗概念

根据上述问题,近年许多学者提出了“TACE 失败/抵抗(TACE failure/refractory)”概念。日本肝脏病学会(JSH)于 2010 年首次定义 TACE 术失败/抵抗[37]:①2 次或 2 次以上 TACE 术后 4 周内 CT 评估见肿瘤不完全坏死(碘油沉积<50%)或新发病灶;②随访过程中出现血管侵犯;③随访中出现肝外转移;④术后肿瘤标志物持续升高。2011 年 HCC 介入治疗国际专家组(EPOIHCC)共识[38]指出,TACE 术失败指 6 个月内同一病灶经 3 次或 3 次以上 TACE 治疗后无效(病灶处于稳定期/进展期)。2014 年欧洲肝病研究学会(EASL)阐述 TACE 抵抗定义时指出,TACE 抵抗定义根据患者接受 TACE 术目的不一而不相同[39],如果 TACE 作为姑息性疗法,稳定期病灶可视为有效结果;如果 TACE 在某些情况下作为治愈手段,稳定期病灶则视为无效结果,可视为发生 TACE 抵抗。2014 年 JSH-日本肝癌研究组(LCSGJ)修订 TACE 抵抗定义[40]:①肝内病灶连续 2 次或 2 次以上经确切超选择 TACE(包括更改化疗药物及重新分析血管)治疗后 1～3 个月内,CT/MRI 复查提示有>50%病灶处于反应不良状态或新发病灶;②术后甲胎蛋白(AFP)持续升高(术后可能有一过性下降);③出现血管侵犯;④出现肝外转移。

2 HCC 患者 TACE 抵抗的治疗

关于 HCC 患者 TACE 抵抗的治疗方案,目前尚无统一标准。有研究提出,采用再行 TACE 治疗评估(ART)评分方法评估患者是否应接受第 2 次 TACE 治疗[41]。Raoul 等[39]主张对 TACE 治疗后出现严重并发症或 Child-Pugh 评分增加患者停止TACE,采用索拉菲尼治疗;对无上述症状患者,术后 4～6 周复查增强 CT 或 MR 时若显示病灶进展,停止 TACE 并采用索拉菲尼治疗,若病灶稳定则计算 ART 评分,ART 评分≥2.5 时停止 TACE 并更换治疗方案,反之继续予 TACE 治疗。但大多数学者倾向于采用索拉非尼治疗[38,42-43]。

2.1 索拉非尼治疗

索拉非尼作为一种分子靶向药物,通过阻断 Raf 信号通路、血管内皮细胞生长因子(VEGF)、血小板衍生生长因子(PDGF)及 c-Kit,起到抗恶性细胞增生、抗血管生成和延缓肿瘤进展的作用[27],已证明可延长 BCLC C 期 HCC 患者生存期[44-45],为该期患者推荐治疗方案[27]。TACE 抵抗概念提出后,JSH 即推荐应用索拉非尼治疗。多项回顾性研究也证明索拉非尼可延长 TACE 抵抗患者生存期。Ogasawara 等[42]在一项回顾性研究中入组 56 例 TACE 抵抗患者,其中转为索拉非尼治疗 20 例,继续 TACE 治疗 36 例,结果显示索拉非尼治疗组、继续 TACE 治疗组平均疾病进展时间(TTP)分别为 22.3 个月、7.7 个月(P=0.001),平均总体生存期(OS)分别为 25.4 个月、11.5 个月(P=0.003);表明索拉非尼可延长 TACE 抵抗患者 TTP 和 OS。Arizumi 等[46]报道类似研究结果,索拉非尼治疗组(32 例)、继续 TACE 治疗组(24 例)平均 OS 分别为 24.7 个月、13.6 个月(P=0.002)。

2.2 经肝动脉灌注化疗

由于 TACE 抵抗治疗中部分患者无法耐受索拉非尼不良反应,如腹泻、皮疹、脱发、手足综合征等[46],一些学者探究其它治疗方法。Iwasa 等[47]回顾性分析顺铂经导管动脉灌注化疗(TAI)治疗 84 例 TACE 抵抗患者的效果,结果显示完全缓解(CR)+部分缓解(PR)即疾病缓解率为 3.6%,CR+PR+疾病稳定(SD)即疾病控制率为 48.8%,平均 OS 为 7.1 个月,1 年生存率为 27%,平均无进展生存期为 1.7 个月。Ikeda 等[43]对比分析索拉非尼与 TAI 治疗TACE 抵抗患者的有效性,索拉非尼治疗组(n=48)、TAI 组(n=66)有效率(CR+PR)分别为 6.3%、1.5%(P=0.40),疾病控制率(CR+PR+SD)分别为 60.4%、28.8%(P=0.001),平均 TTP 分别为 3.9 个月、2.0 个月(P<0.01),平均 OS 分别为 16.4 个月、8.6 个月

($P<0.001$)；认为索拉非尼治疗 TACE 抵抗比 TAI 治疗，可获得更高疾病控制率及更长生存期。

2.3 经肝动脉微球栓塞治疗

有学者认为 TACE 抵抗与栓塞剂应用有关，并非所有 HCC 病灶经栓塞均有明显碘油沉积[48]，且因血流不断冲刷作用，化疗药物会冲入体循环，从而降低治疗效果[49]。鉴于此，Song 等[50]回顾性分析载药缓释微球 DC Bead™ 行 TACE(d-TACE)治疗 10 例传统 TACE 抵抗患者的效果，结果显示有效率(CR+PR)为 100%。但该报道病例数较少，缺乏对照研究，其有效性尚需更多临床研究证明。

2.4 体外放疗

随着适形放疗技术不断发展，Yu 等[51]提出大分割放疗方案治疗 TACE 抵抗，并回顾性分析 50 例确诊的 TACE 抵抗患者经大分割放疗的效果，结果显示 3 年局部无进展生存率为 89.7%，3 年总生存率为 57.4%。

2.5 局部近距离放疗

与体外放疗相比，近距离放疗作为一种治疗 HCC 新方法，具有很多优势[52-55]：①仅需单次植入放射性物质，不需反复多次治疗；②瘤周正常组织放射性损伤小；③可延长放射性物质对肿瘤的杀伤时间。放射性 ^{125}I 粒子植入作为近距离放疗手段之一，越来越广泛地应用于肝癌治疗[56-57]。Nag 等[58]回顾性分析 ^{125}I 粒子植入治疗 64 例肝癌患者，结果显示中位 OS 为 9 个月，1、3、5 年生存率分别为 44%、22%、22%。Lü 等[59]回顾性分析 ^{125}I 粒子植入控制治疗 48 例 TACE 术后残余病灶患者，术后 1 个月随访显示 CR 为 16.7%，PR 为 54.2%，中位 OS 为 15.5 个月，1、2、3 年生存率分别为 75%、45.8%、27.1%。放射性 ^{125}I 粒子植入控制局部肿瘤病灶有很好疗效，但目前尚无其治疗 TACE 抵抗的报道。

3 结语

综上所述，TACE 是中期(BCLC B 期)肝癌标准化治疗方法，但仍有相当部分患者反应不佳，产生 TACE 抵抗。目前对 TACE 抵抗患者进一步治疗尚缺乏统一规范方案。有限的回顾性临床研究提示 TAI、大分割放疗、d-TACE 及索拉非尼是治疗 TACE 抵抗的有效手段，索拉非尼被推荐为目前治疗方案，但仍需更多前瞻性随机对照研究加以证明。放射性 ^{125}I 粒子植入有望成为新治疗方法。

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