

经动脉化疗栓塞(TACE)联合经动脉灌注化疗(HAIC)对比单纯TACE治疗不可切除肝癌的疗效及安全性

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摘要

目的: 比较TACE联合HAIC与单纯TACE方案治疗不可切除肝细胞癌的疗效及安全性。方法: 该项研究为单中心回顾性研究, 选取了2020年8月至2021年8月在重庆医科大学附属第二医院接受了TACE + HAIC或单纯TACE治疗的HCC患者共156人。分为TACE + HAIC方案组80人, 单纯TACE方案组76人。结果: 两组均无患者达到CR, TACE + HAIC组明显高于TACE组的客观缓解率(ORR) (46.3% vs 25.0%, $p = 0.006$)。而两组患者的DCR无明显差异(TACE + HAIC: 92.6% vs TACE: 85.5%, $p = 0.162$)。对两组的ORR与DCR之间进行了单因素logistic回归, 结果显示ORR (OR: 0.387, 95%CI: 0.196~0.765, $p = 0.006$), DCR (OR: 0.479, 95%CI: 0.168~1.368, $p = 0.169$)。以及多因素logistic回归分析显示ORR (OR: 0.291, 95%CI: 0.126~0.674, $p = 0.004$), DCR (OR: 0.550, 95%CI: 0.161~1.876, $p = 0.339$)。结论: TACE + HAIC治疗晚期不可切除肝癌的疗效明显优于单纯TACE治疗。

关键词

TACE, HAIC, HCC

Efficacy and Safety of Transcatheter Arterial Chemoembolization (TACE) Combined with Hepatic Arterial Infusion Chemotherapy (HAIC) Compared with TACE Alone for Unresectable Hepatocellular Carcinoma

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Abstract

Objective: To compare the efficacy and safety of TACE combined with HAIC versus TACE alone regimen for unresectable hepatocellular carcinoma. **Methods:** The study was a single-center retrospective study, and a total of 156 patients with HCC treated with TACE + HAIC or TACE alone at the Second Hospital of Chongqing Medical University from August 2020 to August 2021 were selected. They were divided into 80 in the TACE+HAIC regimen group and 76 in the TACE regimen group. **Results:** No patients in either group achieved CR, and the objective remission rate (ORR) was significantly higher in the TACE+HAIC group than in the TACE group (46.3% vs 25.0%, $p = 0.006$). In contrast, there was no significant difference in DCR between the two groups (TACE + HAIC: 92.6% vs TACE: 85.5%, $p = 0.162$). One-way logistic regression was performed between ORR and DCR in both groups, which showed ORR (OR: 0.387, 95%CI: 0.196~0.765, $p = 0.006$), DCR (OR: 0.479, 95%CI: 0.168~1.368, $p = 0.169$). Multifactorial logistic regression analysis showed ORR (OR: 0.291, 95%CI: 0.126~0.674, $p = 0.004$), DCR (OR: 0.550, 95%CI: 0.161~1.876, $p = 0.339$). **Conclusion:** The efficacy of TACE + HAIC for advanced unresectable hepatocellular carcinoma was significantly better than that of TACE alone.

Keywords

TACE, HAIC, HCC

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1. 背景

肝细胞癌(HCC)是最常见的第六大恶性肿瘤,在中高社会人口指数国家的所有癌症死亡率中排名第四[1]。中国是乙肝大国,中国肝癌患者数量占世界总数的 50% 以上。肝癌在我国恶性肿瘤发病率中排名第四,在我国恶性肿瘤死亡率中排名第二[2]。在肝细胞癌中,治疗的首选是肝切除术[3]。但由于肝癌早期没有任何症状,很多患者确诊为肝癌时已经发展为肝癌晚期,失去了手术的机会。对于晚期的肝癌,欧洲和美国推荐索拉非尼及 TACE 作为一线治疗[3] [4],然而,一些研究表明,HAIC 的中位生存期(OS)比索拉非尼长(7.1 个月 vs 5.5 个月, $p = 0.011$), HAIC 的中位进展时间(TTP)也比索拉非尼长[5]。早在 2014 年,日本肝病学会就推荐使用 HAIC 治疗晚期肝癌伴门静脉癌栓患者,甚至是 Vp4 患者[6]。

肝动脉灌注化疗(Hepatic arterial infusion chemotherapy)是通过经皮穿刺至靶(肝)动脉,通常是经股动脉或桡动脉,然后长期持续灌注化疗药物。由于 HCC 肿瘤主要由肝动脉供血,HAIC 可以在肿瘤内提供更高浓度的化疗药物[7]。既往有许多研究显示了 HAIC 治疗晚期肝癌的疗效及安全性[8] [9] [10] [11],但许多研究都是单独使用 HAIC 或者 TACE,用 TACE + HAIC 方案治疗 HCC 的研究较少,因此本研究旨在对比 TACE + HAIC 与单纯 TACE 治疗晚期不可切除 HCC 的疗效及安全性。

2. 资料与方法

资料:

本研究为单中心的回顾性研究,因此放弃了取得患者知情同意的要求。研究选取了2020年8月至2021年8月在重庆医科大学附属第二医院接受了TACE+HAIC或者单纯TACE治疗的HCC患者共185人。入选标准如下:1)不可切除的肝细胞癌;2)至少有一个可测量直径的肿瘤;3)巴塞罗那分期C期及以下;4)Child-Pugh肝功能评级为A或者B级;5)血小板计数 $\geq 50 \times 10^9/L$;6)白细胞计数 $\geq 3 \times 10^9/L$;7)中性粒细胞绝对数 $\geq 1.5 \times 10^9/L$;8)ECOG评分为0或1。最终156人入选,分为TACE+HAIC组共80人,单纯TACE组共76人。具体流程见图1。

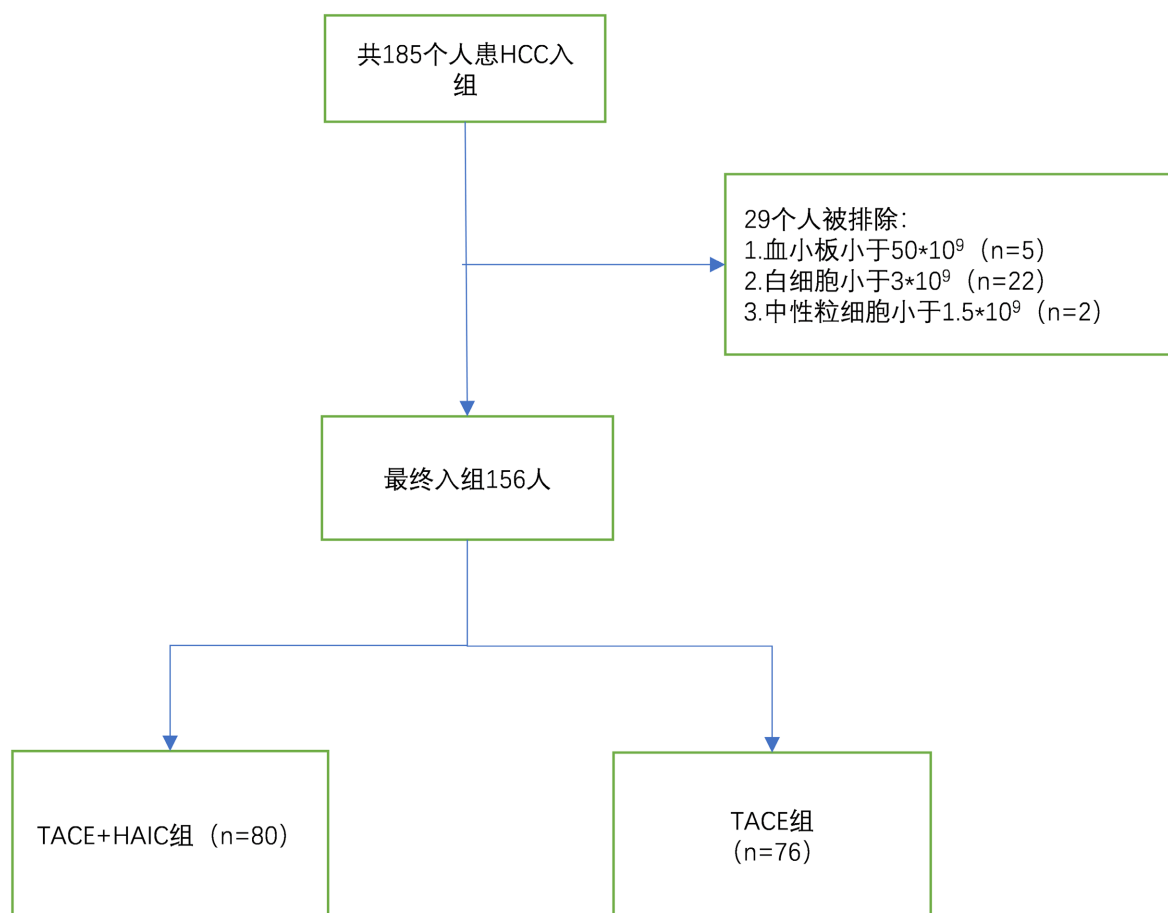


Figure 1. Flowchart summarizes patient inclusion

图1. 患者入选流程图

方法:

单纯TACE患者在治疗时,将导管经皮插入至肝癌的供血动脉,予以碘油,表柔比星,空白微球进行化疗栓塞,结束后拔出导管,压迫止血。每4~6周重复1次,接受4~6次或患者不能忍受为止。TACE+HAIC组患者以同样方式进行动脉化疗栓塞(TACE)后留置动脉导管于靶动脉,返回病房后首先予以奥沙利铂 85 mg/m^2 动脉滴注3h,再予以亚叶酸钙 200 mg/m^2 动脉滴注,最后予以5氟尿嘧啶 2500 mg/m^2 持续微量泵入44h。每4~6周循环一次,接受4~6次或患者不能忍受该治疗方案为止。

疗效判定:治疗前进行基线评价,包括CT、磁共振成像(MRI)、AFP等。疗效评价在治疗后1年进行,

采用实体肿瘤评价标准 mRecist 进行评价。分为完全缓解(CR)、部分缓解(PR)、稳定(SD)和进展(PD)。总随访时间为 12 个月。评价目标包括客观缓解率(ORR)、疾病控制率(DCR)。ORR = CR + PR, DCR = CR + PR + SD。

统计方法:

分类变量采用卡方检验或 fisher 精确检验, 连续变量采用秩和检验, 比较两组基线的差异, 对两组疗效比较采用卡方检验及 logistic 回归, 所有显著性检验均为双侧检验, $p < 0.05$ 差异有统计学意义。所有检验方案由 SPSS26.0 进行。

3. 结果

本研究共纳入患者 156 名, 其中 TACE + HAIC 组 80 人, TACE 组 76 人。对两组患者基线进行比较, 两组患者基线特征无明显差异, p 值均大于 0.05; 其中 BCLC 差异也在可接受范围内($p = 0.075 > 0.05$)。具体情况见表 1。

Table 1. Baseline characteristics

表 1. 基线特征表

	总计 N = 156	TACE N = 76	TACE+HAIC N = 80	p Value
性别				
男	133 (85.3%)	68 (89.5%)	65 (81.3%)	0.148
女	23 (14.7%)	8 (10.5%)	15 (18.7%)	
年龄	54.3 (29~84)	55.6 (29~84)	53.0 (29~71)	0.128
BCLC				
A	18 (11.5%)	12 (15.8%)	6 (7.5%)	0.075
B	74 (47.4%)	39 (51.3%)	35 (43.8%)	
C	64 (41.1%)	25 (32.9%)	39 (48.8%)	
ChildPugh				
A	148 (94.9%)	73 (96.1%)	75 (93.8%)	0.720
B	8 (5.1%)	3 (3.9%)	5 (6.3%)	
免疫				
是	65 (41.7%)	30 (39.5%)	35 (43.8%)	0.588
否	91 (58.3%)	46 (60.5%)	45 (56.3%)	
CauseHCC				
其他	23 (14.7%)	12 (15.8%)	11 (13.8%)	0.931
HBV	130 (83.3%)	63 (82.9%)	67 (83.8%)	
HCV	3 (1.9%)	1 (1.3%)	2 (2.5%)	
肝硬化				
无	27 (17.3%)	10 (13.2%)	17 (21.3%)	0.182
有	129 (82.7%)	66 (86.8%)	63 (78.8%)	
肿瘤数目				
单发	84 (53.8%)	45 (59.2%)	39 (48.8%)	0.190
多发	72 (46.2%)	31 (30.8%)	41 (51.2%)	

Continued

血管受侵				
否	85 (54.5%)	44 (57.9%)	41 (51.3%)	0.405
是	71 (45.5%)	32 (42.1%)	39 (48.8%)	
AFP				
<1000	102 (65.4%)	54 (71.1%)	48 (60.0%)	0.147
≥1000	54 (34.6%)	22 (28.9%)	32 (40.0%)	
治疗次数	2.17	2.29	2.06	0.174

注: BCLC: 巴塞罗那分期; ChildPugh: 肝功能分级; CauseHCC: 肝癌诱发因素; AFP: 甲胎蛋白。

肿瘤反应:

两组均无患者达到 CR, 其中 TACE + HAIC 组达到 PR 的有 37 人(46.3%), SD 为 37 人(46.3%), PD 共 6 人(7.4%)。TACE 组达到 PR, SD, PD 的人数分别为 19 (25.0%), 46 (60.5%), 11 (14.5%)。TACE + HAIC 组明显高于 TACE 组的客观缓解率(ORR), 且有统计学意义(46.3% vs 25.0%, $p = 0.006$)。而两组患者的 DCR 无明显差异(TACE + HAIC: 92.6% vs TACE: 85.5%, $p = 0.162$)具体情况见表 2。对两组的 ORR 与 DCR 之间进行了单因素 logistic 回归, 结果显示 ORR 差异有统计学意义(OR: 0.387, 95%CI: 0.196~0.765, $p = 0.006$), DCR 无显著差异(OR: 0.479, 95%CI: 0.168~1.368, $p = 0.169$)。以及加入了基线表无显著差异的年龄, 性别, 肝硬化, 血管受侵, AFP, Child-Pugh, BCLC, 免疫, 治疗次数等因素后的多因素 logistic 回归分析显示 ORR (OR: 0.291, 95%CI: 0.126~0.674, $p = 0.004$), DCR (OR: 0.550, 95%CI: 0.161~1.876, $p = 0.339$)。具体情况见表 3, 表 4。

不良反应:

两组患者不良反应无显著差异, 多为 1~2 级的不良反应, 无需特殊干预均可自行好转, 3~4 级不良反应经过对症治疗后缓解。两组间均无严重不良反应致死情况。TACE + HAIC 组在血液学不良反应相对较多, 但两组间差异无统计学意义。具体情况见表 5。

Table 2. Tumor response in both groups

表 2. 两组患者的肿瘤反应

	总计	TACE	TACE + HAIC	p Value
CR	0	0	0	—
PR	56 (35.9%)	19 (25.0%)	37 (46.3%)	0.006
SD	83 (53.2%)	46 (60.5%)	37 (46.3%)	0.074
PD	17 (10.9%)	11 (14.5%)	6 (7.4%)	0.162
ORR	56 (35.9%)	19 (25.0%)	37 (46.3%)	0.006
DCR	139 (89.1%)	65 (85.5%)	74 (92.6%)	0.162

注: CR: 完全缓解; PR: 部分缓解; SD: 疾病稳定; PD: 疾病进展; ORR: 客观缓解率; DCR: 疾病控制率。

Table 3. Single and multifactor logistic of two sets of ORRs

表 3. 两组 ORR 单因素及多因素 logistic 回归

治疗方案	单因素 logistic 回归			多因素 logistic 回归		
	OR	95%CI	p Value	OR	95%CI	p Value
TACE	—	—	—	—	—	—
TACE + HAIC	0.387	0.196~0.765	0.006	0.291	0.126~0.674	0.004

Table 4. Single and multifactor logistic of two sets of DCR
表 4. 两组 DCR 单因素及多因素 logistic 回归

治疗方案	单因素 logistic 回归			多因素 logistic 回归		
	OR	95%CI	p Value	OR	95%CI	p Value
TACE	—	—	—	—	—	—
TACE + HAIC	0.479	0.168~1.368	0.169	0.550	0.161~1.876	0.339

Table 5. Adverse reactions
表 5. 不良反应

	TACE		TACE + HAIC		p Value
	Grade1~2	Grade3~4	Grade1~2	Grade3~4	
发热	24 (31.6%)	3 (3.9%)	20 (25.0%)	2 (2.5%)	0.574
疼痛	19 (25.0%)	3 (3.9%)	16 (20.0%)	1 (1.3%)	0.382
呕吐	7 (9.2%)	0 (0.0%)	9 (11.3%)	2 (2.5%)	0.538
白细胞减少	2 (2.6%)	2 (2.6%)	4 (5.0%)	1 (1.3%)	0.665
血小板减少	2 (2.6%)	2 (2.6%)	4 (5.0%)	2 (2.5%)	0.879
中性粒细胞减少	4 (5.3%)	4 (5.3%)	3 (3.8%)	5 (6.3%)	0.926
ALT 升高	5 (6.6%)	1 (1.3%)	5 (6.3%)	1 (1.3%)	1.000
AST 升高	4 (5.3%)	3 (3.9%)	6 (7.5%)	1 (1.3%)	0.562
总胆红素升高	5 (6.6%)	1 (1.3%)	4 (5.0%)	4 (5.0%)	0.431

注：ALT：谷丙转氨酶；AST：谷草转氨酶。

4. 讨论

对于晚期不能手术切除的肝细胞癌，TACE 作为一线治疗方案被广泛接受，甚至在韩国，日本和其他亚洲国家也被推荐用于晚期肝癌合并门静脉癌栓患者的治疗，在日本和韩国的一项多中心前瞻性随机研究中，行 TACE 治疗的完全或部分缓解率为 73%，2 年 OS 率为 75% [12] [13] [14]，而 HAIC 虽不是晚期肝癌推荐的一线治疗方案，但许多研究都表明 HAIC 在治疗晚期肝癌有着不错的疗效[8] [15] [16] [17]。虽然 TACE 联合 HAIC 相关研究相对较少，但也有研究显示 TACE + HAIC 相比与单纯 TACE 能取得更好的疗效，TACE + HAIC 的 ORR 及 DCR 分别为 31.7% 和 81.7% [18]，这与本研究得到的结果相似。本研究中，TACE + HAIC 的 ORR 为 46.3%，DCR 为 92.6%，显示出了相似的疗效结果。本研究中两组患者的不良反应无显著差异，也与既往研究结果相同。TACE + HAIC 在血液学反应更严重可能跟 TACE 术后化疗药物的使用有关，但严重不良反应较少，且经过对症治疗后均可好转。

本研究也存在一定的局限性，首先这是一个单中心的回顾性研究，样本量较少，并且现在晚期肝癌多为综合性治疗，很难保证两组基线完全一致，需要更大样本的前瞻性研究来验证其结果的准确性。其次 TACE 时的栓塞材料及位置会有一些的差异，术后动脉导管保留的位置也会影响其疗效，这种很难保证完全统一。

综上所述，TACE + HAIC 与单纯 TACE 两者在疾病控制率上没有显著差异，但对晚期不可切除肝癌的客观缓解率上 TACE + HAIC 显示出了更好的疗效，且两者安全性可以接受，无明显差异，显示出了 TACE + HAIC 治疗晚期肝癌患者有着更好的疗效。因此，在患者可接受的情况下建议在 TACE 结束后进行动脉灌注化疗。

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