◇ 药物治疗学 ◇

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PD-1/PD-L1 抑制剂联合化疗一线治疗晚期胆道恶性肿瘤的疗效及安全性研究

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摘要　**目的：**探索程序性细胞死亡蛋白-1/其配体-1（programmed cell death protein-1/its ligand-1，PD-1/ PD-L1）抑制剂联合化疗一线治疗晚期胆道恶性肿瘤的疗效及安全性。**方法：**回顾性收集2020 年 8 月至 2022 年 8 月安徽医科大学第一附属医院收治的 33 例经组织病理学确诊的晚期胆道恶性肿瘤患者，根据一线治疗中是否应用 PD-1/PD-L1 抑制剂分为常规化疗组和联合免疫治疗组，每 2 周期进行疗效评价，每周期评价安全性，主要研究终点为无进展生存期（progression-free survival，PFS），次要终点为治疗的安全性。**结果：**33 例患者无完全缓解（complete response，CR）病例，常规化疗组 16 例患者，其中部分缓解（partial response，PR）3 例、疾病稳定（stable disease，SD）6 例、疾病进展（progressive disease，PD）7 例，客观有效率（objective response rate，ORR）为 18.8%，疾病控制率（disease control rate，DCR）为 56.2%。中位 PFS 为 13.1 周。联合免疫治疗组 17 例患者，其中 PR 8 例、SD 5 例、PD 4 例，ORR 为 47.1%，DCR 为 76.5%，中位 PFS 为 21.9 周，优于常规化疗组，且差异具有统计学意义。两组不良反应多为 1-2 级，可耐受，差异均无统计学意义。**结论：**PD-1/PD-L1 抑制剂联合化疗和/或抗血管药物治疗晚期胆道恶性肿瘤疗效确切，安全性良好，PD-1/PD-L1 抑制剂联合化疗治疗晚期胆道恶性肿瘤的治疗模式值得临床进一步探索。

关键词　晚期胆道恶性肿瘤；免疫检查点抑制剂；化疗；PD-1/PD-L1

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胆道恶性肿瘤（biliary tract cancer，BTC）是一种起源于胆管上皮细胞的恶性肿瘤，约占消化道恶性肿瘤 3%[1]。根据发病部位，可将其分为胆管癌（cholangiocarcinoma，CCA）和胆囊癌（gallbladder carcinoma，GCA）。近年来，世界范围内胆管癌的发病率明显上升[2]。胆道恶性肿瘤早期症状多不明显，起病隐匿，发现时多为晚期，晚期胆道恶性肿瘤病情进展迅速，临床治疗手段有限[3]，以吉西他滨或氟脲类为基础的药物化疗是该类病人的基础化疗方案，国内外尚无针对胆道肿瘤标准的一、二线治疗方案的结论，其中位总生存期不足 12 个月[1, 4-5]。

近年来，免疫检查点抑制剂（immune checkpoint inhibitors，ICIs）的应用是肿瘤治疗领域的重大突破性进展[6-7]。ICIs 在胆道恶性肿瘤中也进行了诸多尝试，但整体效果欠佳。有研究表明，免疫检查点抑制剂联合吉西他滨为基础的化疗方案能够让部分患者获益[8-9]。在肝细胞癌的治疗中，免疫治疗联合血管内皮生长因子受体（vascular endothelial growth factor receptor，VEGFR）抑制剂能够让患者生存获益[10-11]，但免疫联合治疗能否应用于晚期胆道恶性肿瘤是临床值得探索的问题。因此，本研究拟探讨真实世界晚期胆道恶性肿瘤免疫联合治疗的疗效及安全性，旨在为该类患者提供更多的治疗选择。

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1　资料与方法

1.1　病例选择及一般资料　回顾性分析安徽医科大学第一附属医院肿瘤内科和中西医结合肿瘤科 2020 年 8 月至 2022 年 8 月收治的 33 例晚期胆道恶性肿瘤患者的临床资料，根据一线治疗中是否应用程序性细胞死亡蛋白-1/其配体-1（programmed cell death protein-1/its ligand-1, PD-1/ PD-L1）抑制剂分为常规化疗组和联合免疫治疗组。

患者纳入标准：（1）年龄 18 周岁或以上；（2）ECOG-PS 评分为 0-2 分；（3）所有患者均经组织病理学确诊，并具有可评估的影像学靶病灶；（4）局部晚期或远处转移；（5）既往未接受过全身抗肿瘤治疗包括化疗、靶向治疗和（或）免疫治疗，或者接受术后辅助化疗≥ 6 个月内复发者；（6）预计生存时间≥ 3 个月；（7）由临床医生判断能耐受化疗及免疫治疗的骨髓、肝肾、心脏、肺、神经系统功能等，无明显抗肿瘤治疗禁忌；（8）本研究经本院医学伦理委员会批准，所有患者入组前均签署抗肿瘤治疗知情同意书。

1.2　方法　常规化疗组 16 例患者中 12 例采用吉西他滨为基础的两药联合方案，联合 5-氟尿嘧啶（5-fluorouracil, 5-FU）类药物，如卡培他滨、替吉奥；顺铂、奥沙利铂；白蛋白紫杉醇等；4 例采用 5-FU 类为基础的两药联合方案，联合白蛋白紫杉醇或奥沙利铂。联合免疫治疗组 17 例患者中 10 例采用卡瑞利珠单抗 200 mg q3w 治疗，4 例采用替雷利珠 200 mg q3w 治疗，1 例采用信迪利单抗 200 mg q3w 治疗，1 例采用特瑞普利单抗 3 mg/kg q2w 治疗，1 例采用恩沃利单抗 150 mg qw 治疗。主要联合的化疗药物包括吉西他滨、铂类、紫杉类、5-FU 类。具体化疗方案及剂量由临床医师根据患者情况进行制定，每 6 ~ 8 周进行一次影像学评估疗效，如果疗效评价为完全缓解（complete response, CR）、部分缓解（partial response, PR）或疾病稳定（stable disease, SD）应继续治疗，治疗至肿瘤进展或出现不可耐受的毒副反应为止。

1.3　疗效和不良反应评价　为评价治疗疗效，肿瘤标志物、CT 或 MRI 需在基线和每治疗 2 周期后进行，其中肿瘤标志物也可每周期进行检查。根据实体瘤疗效评价标准 RECIST 1.1 进行疗效评价，包括 CR、PR、SD、疾病进展（progressive disease, PD）、客观有效率（objective response rate, ORR）、疾病控制率（disease control rate, DCR）。CR: 所有目标病灶均消失；PR: 基线病灶长径总和缩小≥30%；SD: 基线病灶长径总和有缩小但未达到 PR 或有增加但未达到 PD；PD: 基线病灶长径总和增加≥20% 或出现新病灶；ORR: 治疗期间获得 CR 和 PR 患者的百分率；DCR: 治疗期间获得 CR、PR 和 SD 患者的百分率；无进展生存期（progression-free survival, PFS）是指从第一次接受治疗开始至疾病出现进展或出现任何原因导致患者死亡的时间。所有的药物不良反应按照 NCI 4.03 版本进行分级。

1.4　统计学处理　采用 R4.05 统计软件进行分析。本研究主要终点为 PFS，次要终点为并发症的发生率。组间差异比较采用卡方检验，Kaplan-Meier 法绘制生存曲线，Log-rank 检验进行统计学分析，不良反应采用 Fisher's 精确概率法检验。P<0.05 表示差异有统计学意义。

2　结果

2.1　基线特征及治疗情况　常规化疗组共纳入 16 例患者，男性 7 例，女性 9 例。4 例患者进行了微卫星稳定性（microsatellite stable, MSS）和/或 PD-L1 检测，皆为 MSS 型，其中 2 例行 PD-L1 检测，1 例 PD-L1 表达阳性<1%，1 例 PD-L1 90% 表达阳性。联合免疫治疗组共纳入 17 例患者，男性 12 例，女性 5 例，4 例患者进行了 MSS 和/或 PD-L1 检测，其中 1 例行 PD-L1 检测，其表达阳性<1%。患者一般特征见 Tab.1。截至 2022.08.31，33 例患者因疾病进展出组，所有患者均可接受安全性分析。

2.2　近期疗效　33 例患者均可评估疗效，见 Tab.2，常规化疗组 16 例患者，其中 PR 3 例、SD 6 例、PD 7 例，ORR 18.8%，DCR 56.2%。联合免疫治疗组 17 例患者，其中 PR 8 例、SD 5 例、PD 4 例，ORR 47.1%，DCR 76.4%。ORR 和 DCR 在两种治疗方式之间的差异均无统计学意义。

2.3　远期疗效　33 例患者均因疾病进展出组，常规化疗组患者中位 PFS 为 13.1 周，联合免疫治疗组中位 PFS 为 21.9 周。K-M 曲线提示联合免疫治疗组的患者 PFS 显著优于单纯化疗治疗的患者，见 Fig.1A。将相关协变量，如性别、年龄、肿

Tab.1 Basic clinical characteristics of included patients

Item	Chemotherapy (*n*=16)	Chemotherapy combined with immunotherapy (*n*=17)	*P*-value
Gender			
Male	7 (43.8%)	12 (70.6%)	0.228
Female	9 (56.3%)	5 (29.4%)	
Years			
Mean (SD)	59.4 (9.59)	57.8 (7.72)	0.601
Median[Min, Max]	57.5 [42.0, 75.0]	57.0 [45.0, 71.0]	
Tumor type			
Gallbladder cancer	6 (37.5%)	5 (29.4%)	0.902
Cholangiocarcinoma	10 (62.5%)	12 (70.6%)	
Tumor grade			
Poorly differentiated	5 (31.3%)	6 (35.3%)	1
Moderately differentiated	11 (68.8%)	11 (64.7%)	
MSS			
Stable	4 (25.0%)	4 (23.5%)	1
Unclear	12 (75.0%)	13 (76.5%)	
Follow-up time (weeks)			
Mean(SD)	41.4 (23.9)	35.4 (15.9)	0.41
Median[Min, Max]	39.5 [10.3, 96.6]	30.1 [12.4, 69.4]	

Tab.2 Evaluation of treatment response in two patient groups

Item	Chemotherapy (*n*=16)	Chemotherapy combined with immunotherapy (*n*=17)	*P*-value
PR			
No	13 (81.3%)	9 (52.9%)	0.176
Yes	3 (18.8%)	8 (47.1%)	
SD			
No	10 (62.5%)	12 (70.6%)	0.902
Yes	6 (37.5%)	5 (29.4%)	
PD			
No	9 (56.3%)	13 (76.5%)	0.389
Yes	7 (43.8%)	4 (23.5%)	
DCR	9 (56.2%)	13 (76.4%)	0.282
ORR	3 (18.8%)	8 (47.1%)	0.176

瘤类型等纳入关于 PFS 的 Cox 多因素回归分析，提示治疗方式的选择是影响 PFS 的独立危险因素（化疗联合免疫 *vs.* 化疗：HR 0.28, 95%CI: 0.11 ~ 0.70, *P*=0.007）。见 Fig.1B, Tab.3。

2.4 安全性 患者不良反应发生情况详见 Tab.4。纳入患者未见严重不良反应而终止治疗。最常见的不良反应有白细胞减少、中性粒细胞减少，血小板减少、乏力、纳差等。多为 1-2 级，3-4 级不良反应发生率低。联合免疫治疗组不良反应发生率与常规化疗组相比，差异无统计学意义。

3 讨论

胆道恶性肿瘤发病率低，异质性高，侵袭性强，临床治疗手段有限，治疗效果差。2021 年中

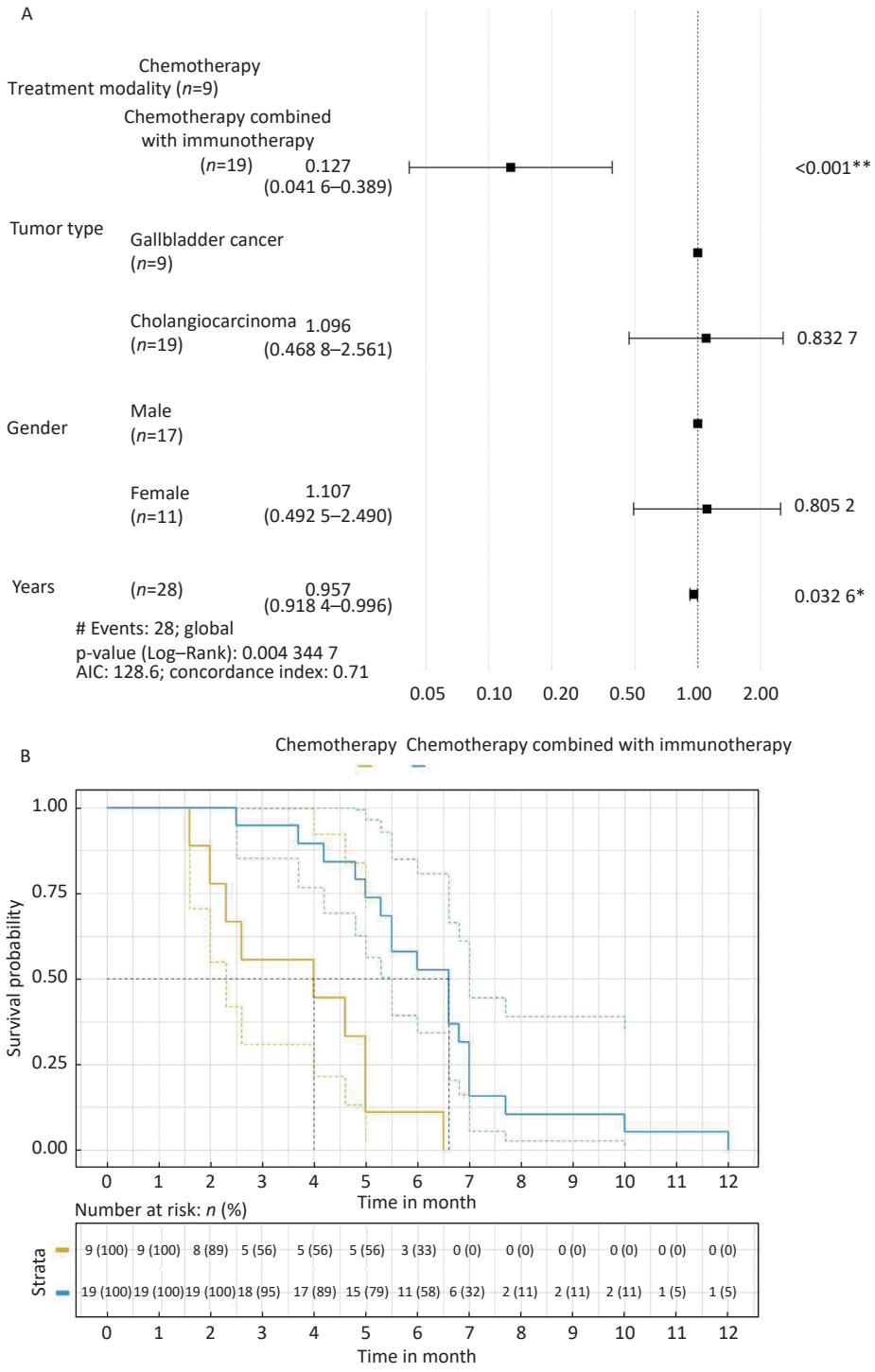


Fig.1 Cox regression analysis of progression-free survival in two patient groups

A: effects of two different treatment approaches on progression-free survival (PFS) in patients with cholangiocarcinoma. Chemotherapy combined with immunotherapy significantly prolonged PFS in patients with cholangiocarcinoma (chemotherapy combined with immunotherapy *vs.* chemotherapy: HR 0.28, 95%CI: 0.11-0.70, *P*=0.007). B: multivariate Cox regression analysis showed that the choice of treatment was an independent risk factor for PFS time in imaging patients.

国临床肿瘤学会(Chinese Society of Clinical Oncology, CSCO)指南Ⅰ级推荐的3个晚期胆道恶性肿瘤一线标准化疗方案分别为：吉西他滨+顺铂(GP)、卡培他滨+奥沙利铂(XELOX)和吉西他滨+替吉奥(GS)。其中ABC-02关于晚期胆道癌的Ⅲ期临床研究确立了吉西他滨联合顺铂作为晚期

Tab.3 Multivariate Cox regression analysis

Item		No.	HR (Univariable)	HR (Multivariable)
Treatment	Chemotherapy	16 (48.5%)		
	Chemotherapy combined with immunotherapy	17 (51.5%)	0.37 (0.17-0.80, *P*=0.012)	0.28 (0.11-0.70, *P*=0.007)
Gender	Male	19 (57.6%)		
	Female	14 (42.4%)	1.76 (0.84-3.71, *P*=0.133)	1.34 (0.52-3.43, *P*=0.545)
Years		58.5 ± 8.6	0.99 (0.95-1.03, *P*=0.575)	0.97 (0.93-1.01, *P*=0.183)
Tumor type	Gallbladder cancer	11 (33.3%)		
	Cholangiocarcinoma	22 (66.7%)	1.24 (0.59-2.59, *P*=0.574)	1.02 (0.46-2.26, *P*=0.970)
Tumor grade	Poorly differentiated	11 (33.3%)		
	Moderately differentiated	22 (66.7%)	2.01 (0.88-4.62, *P*=0.100)	2.12 (0.82-5.49, *P*=0.121)
MSI	Stable	8 (24.2%)		
	Unclear	25 (75.8%)	0.92 (0.40-2.08, *P*=0.834)	0.88 (0.37-2.13, *P*=0.784)

Tab.4 Incidence of treatment-related adverse events in two treatment modalities

Adverse event	Chemotherapy group (*n*=16)	Chemo-immunotherapy group (*n*=17)	*P*-value
Emesis			
None	7 (43.8%)	8 (47.1%)	0.508
Grade 1	3 (18.8%)	6 (35.3%)	
Grade 2	5 (31.3%)	2 (11.8%)	
Grade 3	1 (6.3%)	1 (5.9%)	
Fatigue			
None	6 (37.5%)	7 (41.2%)	0.276
Grade 1	4 (25.0%)	7 (41.2%)	
Grade 2	6 (37.5%)	2 (11.8%)	
Grade 3	0 (0%)	1 (5.9%)	
Neutropenia			
None	5 (31.3%)	5 (29.4%)	0.249
Grade 1	5 (31.3%)	9 (52.9%)	
Grade 2	3 (18.8%)	0 (0%)	
Grade 3	3 (18.8%)	3 (17.6%)	
Leukopenia			
None	5 (31.3%)	5 (29.4%)	0.249
Grade 1	5 (31.3%)	9 (52.9%)	
Grade 2	3 (18.8%)	0 (0%)	
Grade 3	3 (18.8%)	3 (17.6%)	
Thrombocytopenia			
None	7 (43.8%)	7 (41.2%)	0.23
Grade 1	4 (25.0%)	8 (47.1%)	
Grade 2	3 (18.8%)	0 (0%)	
Grade 3	2 (12.5%)	2 (11.8%)	
Rash			

Continued from Tab. 4

Adverse event	Chemotherapy group (*n*=16)	Chemo-immunotherapy group (*n*=17)	*P*-value
None	11 (68.8%)	13 (76.5%)	0.516
Grade 1	4 (25.0%)	3 (17.6%)	
Grade 2	1 (6.3%)	0 (0%)	
Grade 3	0 (0%)	1 (5.9%)	
Immune-related hepatitis			
None	16 (100%)	14 (82.4%)	NA
Grade1	0 (0%)	2 (11.8%)	
Grade 2	0 (0%)	1 (5.9%)	
AST elevated			
None	12 (75.0%)	12 (70.6%)	0.681
Grade1	2 (12.5%)	3 (17.6%)	
Grade 2	1 (6.3%)	0 (0%)	
Grade 3	1 (6.3%)	2 (11.8%)	
ALT elevated			
None	12 (75.0%)	12 (70.6%)	0.681
Grade 1	2 (12.5%)	3 (17.6%)	
Grade 2	1 (6.3%)	0 (0%)	
Grade 3	1 (6.3%)	2 (11.8%)	
Hand-Foot Syndrome (HFS)			
None	14 (87.5%)	15 (88.2%)	0.571
Grade 1	1 (6.3%)	1 (5.9%)	
Grade 2	0 (0%)	1 (5.9%)	
Grade 3	1 (6.3%)	0 (0%)	
Diarrhea			
None	15 (93.8%)	15 (88.2%)	NA
Grade 1	1 (6.3%)	1 (5.9%)	
Grade 2	0 (0%)	0 (0%)	
Grade 3	0 (0%)	1 (5.9%)	
Hypertension			
None	16 (100%)	13 (76.5%)	0.232
Grade 1	0 (0%)	2 (11.8%)	
Grade 2	0 (0%)	1 (5.9%)	
Grade 3	0 (0%)	1 (5.9%)	
Localized pneumonia			
None	16 (100%)	15 (88.2%)	NA
Grade 1	0 (0%)	1 (5.9%)	
Grade 2	0 (0%)	1 (5.9%)	
Hyperthyroidism			
None	16 (100%)	16 (94.1%)	NA
Grade 1	0 (0%)	1 (5.9%)	
Myositis			
None	16 (100%)	15 (88.2%)	NA
Grade 1	0 (0%)	2 (11.8%)	

胆管癌患者的全球标准一线治疗方案[12-13], 但中　　位生存时间也仅有 11.7 个月[14]。

近年随着分子生物学、免疫学及基因工程技术的快速发展，国内外关于肿瘤的免疫治疗已取得很大突破，以 PD-1/PDL1 抑制剂为主的 ICIs 在胆道恶性肿瘤中也进行了诸多尝试[15]，初步获得可喜的抗肿瘤治疗效果，为胆道肿瘤的治疗带来了新的希望。但仍面临 ORR 低及耐药等治疗瓶颈，还未完全取得突破性进展，只在少数晚期胆道恶性肿瘤病人中见到疗效[16-17]，单药的治疗效果依然有限。

临床前研究结果表明化疗可通过增加肿瘤细胞 HLA1 表达，促进肿瘤细胞释放细胞因子，诱导树突状细胞成熟，最终增强 T 细胞肿瘤杀伤能力来帮助恢复免疫监测以增强内源性免疫应答[18]，这一观点得到临床研究的进一步证实。胆道恶性肿瘤具有显著的瘤间或瘤内异质性[19]，近 40% 的患者有潜在靶向的基因突变，具有靶向治疗的可能[20]。靶向治疗包括抗血管生成等药物，主要是针对肿瘤微环境，积累临床前研究和临床证据证明通过免疫治疗联合靶向抑制血管生成药物可增强 PD1/PDL1 免疫治疗的抗肿瘤疗效[14, 21]。在胃癌等多种恶性肿瘤中，ICIs 联合化疗显示出良好的抗肿瘤活性和安全性[22]，理论上 ICIs 联合化疗、靶向治疗、局部治疗以及其他免疫治疗，能够提高晚期胆道恶性肿瘤病人治疗效果，改善预后，可能是未来探索晚期胆道恶性肿瘤治疗的一个重要研究方向。然而，晚期胆道恶性肿瘤中，关于联合使用 ICIs 和化疗的数据很少。因此，研究者开始探索 ICIs 联合化疗、靶向治疗、局部治疗及其他免疫治疗的可行性。

相关临床研究证实 ICIs 联合化疗能够明显提高治疗反应率及延长晚期胆道恶性肿瘤病人生存时间[23]，2020 年欧洲肿瘤内科学会（European Society for Medical Oncology, ESMO）年会上，Li 等报告特瑞普利单克隆抗体联合化疗作为晚期胆道肿瘤一线治疗的一项开放标签Ⅱ期临床研究（JS001-ZS-BC001）[24]，研究共招募 39 例晚期胆道恶性肿瘤病人，34 例病人的缓解率可评价，其中 7 例（20.6%）达到 PR，22 例（64.7%）为 SD，DCR 为 85.3%，所有病人均为 MSS，中位随访时间为 10.0 个月，中位 PFS 为 6.7 个月，中位总生存期尚未达到。免疫治疗联合化疗能否一线应用于晚期胆管癌是临床值得探索的问题，因此，本研究拟探讨真实世界晚期胆管癌采用一线免疫治疗的疗效及安全性，以期为该类患者提供更多的治疗选择。本研究中常规化疗组 ORR 为 18.8%，DCR 为 56.2%。联合免疫治疗组 ORR 为 47.1%，DCR 为 76.4%。ORR 和 DCR 差异均无统计学意义。常规化疗组患者中位 PFS 为 13.1 周，联合免疫治疗组中位 PFS 为 21.9 周。回归曲线提示化疗联合免疫治疗组患者的 PFS 显著优于单纯化疗治疗后的患者，并且并发症可控，安全性较好。

本研究表明在真实世界中患者多选择国产 PD-1 抑制剂，这些药物都在胆道恶性肿瘤中进行了相关研究，并显示了较好的抗肿瘤疗效，安全性良好。由于肿瘤复杂的免疫微环境，目前在胆道恶性肿瘤中尚未发现明确的生物学标记物可以临床预测或评估免疫治疗的效果[25-26]。组织学检测 PDL1 的表达是否能预估患者对 ICIs 的效果，目前尚不明确。也有研究表明可以通过外周血 RNA 测序的手段判断患者对免疫治疗的敏感性[27]。Weinberg 等对 352 例胆道恶性肿瘤患者行微卫星不稳定性（microsatellite instability, MSI）检测发现，只有 2% 的病人为错配修复功能缺陷/高度微卫星不稳定（dMMR/MSI-H）[28]。同样，Goeppert 等通过研究 308 例胆道恶性肿瘤病人样本发现只有 1.3% 的病人为 dMMR/MSI-H[29]。这些研究与前述临床试验报道结果基本一致，即 dMMR/MSI-H 在胆道恶性肿瘤中发生率很低，因此其并不是一个理想的预测免疫治疗效果的生物标记物。

本研究的主要局限性在于研究为回顾性设计，目前由于大多数免疫检查点抑制剂用作二线治疗，但是其作为难治性胆道恶性肿瘤患者的单药治疗疗效有限。我们的数据为化疗联合免疫治疗作为一线治疗胆道恶性肿瘤的一种替代方案初步提供了依据，以期为下一步开展前瞻性多中心随机研究提供重要根据。

综上，在胆道肿瘤领域，免疫检查点抑制剂联合化疗仍处于临床试验阶段，但是免疫和化疗的组合，给晚期胆道肿瘤病人带来了新的希望，但目前缺乏可以临床预测治疗效果的组织学标记物，因此，探索合理的联合方案以及寻找有效的分子标记，仍是临床迫切需要解决的问题。

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Efficacy and safety of PD-1/PD-L1 inhibitors combined with chemotherapy in the treatment of advanced biliary malignancies in the first line of chemotherapy

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ABSTRACT **AIM**: To explore the efficacy and safety of programmed cell death protein-1/its ligand-1 (PD-1/PD-L1) inhibitors combined with chemotherapy in the treatment of advanced biliary malignancies in the first line of chemotherapy. **METHODS**: A retrospective collection of 33 patients with advanced biliary malignant tumors confirmed by histopathology in the First Affiliated Hospital of Anhui Medical University from August 2020 to August 2022 were retrospectively collected, and they were divided into chemotherapy group and chemotherapy combined with PD-1/PD-L1 inhibitor group, and the efficacy was evaluated every 2 treatment cycles, and the safety was evaluated every cycle. The first outcome is PFS and the secondary endpoint is the safety of treatment. **RESULTS**: Among 16 patients in the chemotherapy group, there were 3 PR cases, 6 SD cases and 7 PD cases, with an ORR rate of 18.8% and a DCR rate of 56.2%. The median PFS was 13.1 weeks. Among 17 patients in the immunotherapy group, there were 8 PR cases, 5 SD cases and 4 PD cases. The ORR rate was 47.1%, the DCR rate was 76.5%, and the median PFS was 21.9 weeks, which was better than the chemotherapy alone. Most of the adverse effects in the two groups were 1-2 grade tolerable, and the difference was not statistically significant. **CONCLUSION**: PD-1/PD-L1 inhibitors combined with chemotherapy and/or antivascular drugs for advanced biliary malignancies have a definite efficacy and is safety, and the treatment with PD-1/PD-L1 inhibitors combined with chemotherapy for advanced biliary malignancies deserves further clinical exploration.

KEYWORDS advanced biliary malignancies; Immune checkpoint inhibitors; chemotherapy; PD-1/PD-L1