中文題目：比較肝動脈灌注化學治療、標靶藥物、放射線治療在晚期肝癌合併大血管侵犯病患的治療效果之真實世界研究

英文題目：A real-world study in efficacy comparisons of hepatic arterial infusion chemotherapy, tyrosine kinase inhibitor and radiotherapy in advanced hepatocellular carcinoma with macrovascular invasion

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Background: Hepatocellular carcinoma (HCC) is one of the common digestive cancers in Taiwan and the third leading cause of cancer-related deaths worldwide. Portal vein tumor thrombosis (PVTT) is present in 10-40% of HCC patients at diagnoses, which usually results in worsening liver function, higher incidence of blood metastasis, complications associated with portal hypertension, and intolerance to treatment. In the past, Sorafenib was the only recommended therapy in HCC patients with PVTT by guidelines but the limited effectiveness. Recently, numerous phase-III trials have reported different agents beyond Sorafenib with promising anti-tumor activities and safety. However, the consensus for the treatment of such patients with advanced HCC is limiting. Our study aims to recognize a anti-tumor agent with better efficacy and acceptable safety for patients experiencing HCC complicated with PVTT.

Method: Adults diagnosed with HCC, who treated hepatic arterial infusion chemotherapy (HAIC), from November 2016 to December 2020 at National Cheng Kung University Hospital were retrospectively included. Exclusion criteria included patients without macrovascular invasion, those diagnosed with hepato-cholangiocarcinoma, those died prior to the first radiographic survey, those with Vp1 or Vp2 invasion, those with hepatic vein tumor thrombus or atypical image pattern of tumor thrombus, and those receiving HAIC combined with other regimens (such as radiofrequency thermal ablation or immunotherapy). The eligible patients were categorized in the following groups: (i)HAIC alone, (ii)HAIC plus tyrosine kinase inhibitor (TKI), and (iii) HAIC, TKI, plus radiotherapy. The assessed outcomes included the progression-free survival (PFS), overall survival time, objective response rate (ORR), and adverse reaction. We evaluated the radiologic responses of the tumors by modified Response Evaluation Criteria in Solid tumors (mRECIST). The outcomes between three groups were compared by the Scheffe's multiple comparison test. In multivariable analyses, the variable ($P < 0.05$ in univariate analysis) and the propensity score, consisted of the patient age, the Eastern Cooperative Oncology Group (ECOG) score, Child–Pugh stage, Cancer of the Liver Italian Program (CLIP) score,

were forced entry in the Cox-regression model.

Results: The total 69 patients were categorized in the groups of HAIC alone (14 patients, 20.3%), HAIC plus TKI (39, 56.5%), and HAIC, TKI, plus radiotherapy (16, 23.2%). A significantly dissimilar proportion of AFP>400 between the HAIC alone, HAIC plus TKI, and HAIC, TKI, plus radiotherapy groups (66.67% vs. 42.86% vs. 20%) was disclosed. The higher proportion of Child–Pugh stage A in the HAIC plus TKI (82.05%) and HAIC, TKI, plus radiotherapy (93.75%) groups was exhibited, compared to that in the HAIC alone group (64.29%). The higher proportion of the Cancer of the Liver Italian Program (CLIP) = 2-5 in the HAIC alone (100%) and HAIC plus TKI (92.31%) groups was observed, compared to that in the HAIC, TKI, plus radiotherapy group (68.75%). In further analyses for outcomes, the significantly shorter median (95% CI) of the overall survival time in the HAIC alone (3.3 [1.9-4.8] months) was discovered, compared to that in HAIC plus TKI (13.8 [6.0-15.8] months) (P = 0.024), or HAIC, TKI, plus radiotherapy (14.5 [8.8-23.7] months) (P = 0.015) groups, respectively. However, no significant different (P = 0.999) between the HAIC plus TKI and HAIC, TKI, plus radiotherapy groups was noticed. The lower median (95% CI) of the PFS in the HAIC alone group (2.1 [0.6-2.9] months) was exhibited (P = 0.002), compared to that in the HAIC, TKI, plus radiotherapy group (11.3 [5.5-17.9] months). But no significant different (P = 0.263) in median (95% CI) of the PFS between the HAIC alone and HAIC plus TKI (3.2 [2.2-5.4] months) group was disclosed, and that in the HAIC plus TKI and HAIC, TKI, plus radiotherapy groups was similar (P = 0.528). On the aspect of radiologic responses of the tumors, lower Vessel ORR in the HAIC alone group than that in the HAIC, TKI, plus radiotherapy group (P = 0.010), but no significant different between the HAIC alone and HAIC plus TKI groups (P = 0.622). The patient proportion of adverse events in three group revealed no statistically different (P = 0.500). After adjusting the propensity score consisted of the patient age, the Eastern Cooperative Oncology Group (ECOG) score, Child–Pugh stage, Cancer of the Liver Italian Program (CLIP) score, Cox regression model revealed the adjusted hazard ratio (AHR) (95% CI) for mortality in the HAIC plus TKI and HAIC, TKI, plus radiotherapy groups were respectively 0.17 (0.08 – 0.40) and 0.31 (0.12 – 0.81), compared to the HAIC alone group. The AHR (95% CI) for PFS in the HAIC plus TKI and HAIC, TKI, plus radiotherapy groups were respectively 0.27 (0.13 – 0.57) and 0.21 (0.08 – 0.54), compared to the HAIC alone group.

Conclusion: Compared to the HAIC alone group, our study revealed the significant longer overall survival time in the HAIC plus TKI and HAIC, TKI, plus radiotherapy groups, the longer PFS in the HAIC, TKI, plus radiotherapy group, and the more favorable vessel ORR in the HAIC, TKI, plus radiotherapy group. In sum, compared to HAIC monotherapy, combination therapy with TKI, radiotherapy, or both might impart benefits in patients with advanced HCC, with the lack of different in

the occurrences of adverse events. Accordingly, the ideal strategy for patients with advanced HCC with macrovascular invasion might be multimodal, using a combination of several locoregional therapy and personalized systemic therapy. However, a prospective randomized controlled trial involving the larger patient population is needed for evaluating the efficacy of HAIC combination therapy in the future.