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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Hepatic arterial infusion chemotherapy combined with toripalimab and surufatinib for the treatment of advanced intrahepatic cholangiocarcinoma

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PURPOSE

The aim of the present study is to report the clinical results of patients with advanced intrahepatic cholangiocarcinoma (ICC) who received combination therapy of hepatic arterial infusion chemotherapy (HAIC), toripalimab and surufatinib.

METHODS

The study cohort consisted of 28 patients with advanced ICC who were treated with HAIC (mFOLFOX6 regimen, Q3W) in combination with intravenous toripalimab (240 mg, Q3W) and oral surufatinib (150 mg, once daily). The cohort had 14 male and 14 female patients. The baseline characteristics of the study cohort were obtained. The tumor response and drug-associated toxicity were assessed and reported.

RESULTS

During the follow-up period (median follow-up time: 11.3 months; range: 4–19 months), four patients died of tumor progression. The objective response rate and disease control rate were 58% and 79%, respectively. The mPFS was 9.5 months, and the overall survival rate was 83.3%. The most frequent adverse events were nausea and vomiting (100%) and abdominal pain (85.7%). Serious complications related to death were not observed.

CONCLUSION

The combination treatment schedule for advanced ICC demonstrated positive efficacy and safety profiles.

CLINICAL SIGNIFICANCE

This study provides promising clinical guidance for the treatment of advanced cholangiocarcinoma and is expected to modify the treatment strategy for this disease.

KEYWORDS

Intrahepatic cholangiocarcinoma, hepatic arterial infusion chemotherapy, toripalimab, surufatinib

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Carcinoma of the biliary tract can be classified according to the tumor location as either intrahepatic cholangiocarcinoma (ICC) or extrahepatic cholangiocarcinoma. ICC is the second most common primary liver cancer after hepatocellular carcinoma (HCC), and it accounts for 5%–10% of primary malignancies of the liver.[1] The first-line treatment for ICC is surgical resection. However, approximately 75% of ICCs are diagnosed at an advanced stage, and surgery is not possible for these patients.[2] As a result, the overall prognosis for ICC is very poor, with a median survival of less than 4 months for patients not treated through surgery.[3,4] The current preferred first-line chemotherapy for locally advanced ICC is gemcitabine plus cisplatin (GEMCIS). However, the reported median survival for patients with advanced ICC treated with GEMCIS is only 11.7 months.[5] Therefore, new therapeutic strategies for advanced ICC are needed.

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Hepatic arterial infusion chemotherapy (HAIC) is a well-established transcatheter therapy for hepatic malignancies. With the use of an intraarterially inserted catheter, HAIC may effectively deliver highly concentrated doses of chemotherapy to the tumor bed while sparing the surrounding liver parenchyma.[6] HAIC has been demonstrated to be safe and effective for the treatment of advanced liver-confirmed and unresectable ICC.[7] Given the promising efficacy of targeted therapy and immunotherapy in various malignant tumors, the combination of HAIC with tyrosine kinase inhibitors (TKIs) and programmed cell death protein 1 (PD-1) inhibitors for treating advanced ICC has recently been investigated.[8,9]

Toripalimab is a humanized anti-PD-1 immunoglobulin G4 (IgG4) monoclonal antibody. This drug has demonstrated promising efficacy and safety profiles for treating urologic cancer, melanoma, and gastric cancer. Surufatinib is a small molecule inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3, fibroblast growth factor receptor (FGFR) 1, and colony-stimulating factor 1 receptor. Similar to toripalimab, surufatinib has demonstrated promising clinical efficacy and positive tolerability and safety profiles in patients with advanced solid tumors, such as neuroendocrine neoplasms and thyroid tumors. Recently, the use of toripalimab and surufatinib for treating unresectable ICC has been reported.[10,11]

However, the use of HAIC plus toripalimab and surufatinib for the treatment of unresectable ICC has not yet been reported. Therefore, we conducted this study to explore the efficacy and safety of this triple combination treatment for the treatment of unresectable ICC.

Methods

Our study was a retrospective cohort study. The clinical outcomes of patients with advanced ICC who received HAIC + toripalimab + surufatinib maintenance combination therapies between July 2021 and Oct 2023 at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, were analyzed (Figure 1). The inclusion criteria before treatment were (1) age >18 years, (2) histologically confirmed diagnosis of ICC through ultrasonic-guided biopsy, (3) previous systemic and/or locoregional therapy, (4) Eastern Cooperative Oncology Group (ECOG) performance status 0–2, (5) tumor size evaluable using the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) guidelines,[12] (6) liver, renal, and hematological functions compatible with chemotherapy, and (7) life expectancy ≥3 months. Patients were excluded if they had (1) severe infection or heart, liver, or lung failure, (2) other malignant tumors, (3) uncontrolled ascites, or (4) incomplete medical information or were lost to follow-up.

Main points

- The current first-line intravenous chemotherapy regimen for advanced intrahepatic cholangiocarcinoma (ICC) is deemed unsatisfactory due to its short survival period.
- Tyrosine kinase inhibitors, whether used alone or in combination with immunotherapy, have shown limited efficacy in treating advanced ICC.
- Combining hepatic arterial infusion chemotherapy with toripalimab and surufatinib has demonstrated a significant improvement in the survival period of patients with advanced ICC.

All patients were informed of the purpose of this study, and written consent was obtained. All study protocols were approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (UHCT-IEC-SOP-014-01-02, 2023/07/20) in accordance with the 1975 Declaration of Helsinki.

The baseline characteristics included the patients' demographics, presence of extrahepatic metastases, previous therapies, tumor stage, tumor dimension determined through enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI), and tumor marker levels [carbohydrate antigen 19-9: (CA19-9)].

Treatment procedures and regimens

To perform HAIC, an intraarterial catheter was inserted through the femoral artery using the method described by Irie.[13] A 5F catheter was inserted through the right femoral artery using the Seldinger method. After localization of the ICC, a 5F heparin-coated polyurethane catheter (Braun Medical, Chasseneuil du Poitou, France) was placed at the depth of the gastroduodenal artery (3–5 cm from the origin) to avoid dislocation of the catheter tip, and a side hole (2–3 mm in a longitudinal direction) was made at the level of the common hepatic artery with scissors. The other end of the catheter was connected to the injection port, which was implanted in a subcutaneous pocket created in the right thigh. The gastroduodenal artery and right gastric artery were occluded with steel coils to prevent gastroduodenal injury by the chemotherapeutic agents (Figure 2).

When the blood supply to the HCC stemmed partly from the extrahepatic artery (e.g., a replaced/accessory right hepatic artery from the superior mesenteric artery, replaced/accessory left hepatic artery from the left gastric artery, or other extrahepatic collateral vessels), the artery was first embolized with coils to redistribute the flow of the whole hepatic artery perfusion from multiple arteries to a single artery. This step ensured effective hepatic intraarterial infusion through a single infusion catheter. In this study, arterial port implantation was not suitable for 20 patients as a result of vascular anatomical variation (e.g., the right gastric artery could not be embolized). Therefore, an alternative approach was used to temporarily insert the catheter, and the catheter was removed after chemotherapy.

In the present study, we used an mFOLFOX6 regimen for HAIC (oxaliplatin: 85 mg/m^2 for 2 h on day 1; calcium folinate: 200 mg/m^2 for 2 h on day 1; 5-Fu: 400 mg/m^2 for bolus

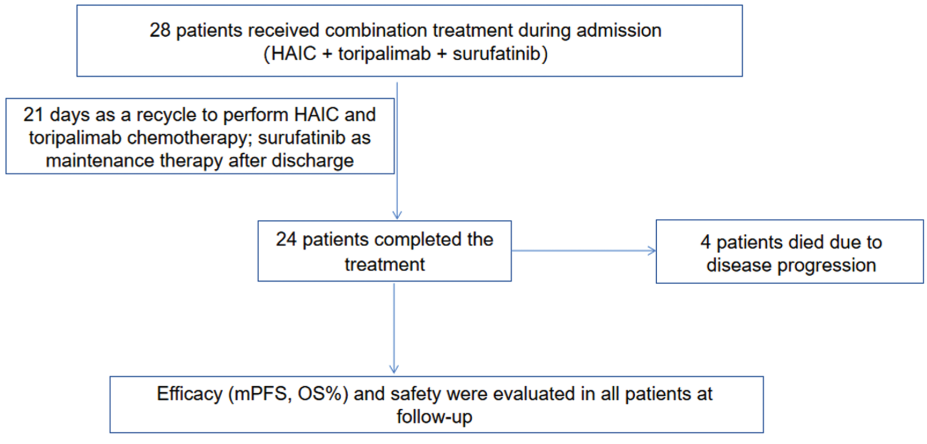

Figure 1. Study treatment flowchart. HAIC, hepatic arterial infusion chemotherapy; mPFS, median progression-free survival; OS, overall survival.

on day 1, followed by 2400 mg/m^2 for 46 h; Q3W). Following HAIC therapy, the patients also received intravenous toripalimab (240 mg on day 3, Q3W) and oral surufatinib (150 mg, once daily). The treatment was performed until unacceptable toxicity or disease progression occurred (Figure 3). Toxicity was recorded and evaluated in accordance with the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE; version 5.0) guidelines.

Tumor response

The disease responses after therapy were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Every two cycles, the response to therapy was assessed using RECIST through CT or MRI. A CR was defined as the complete disappearance of all target lesions, a PR was defined as a ≥30% decrease in the maximum diameter of the target lesion compared with the baseline maximum diameter, PD was defined as a ≥20% increase in the maximum diameter of the target lesion, and SD was defined as disease meeting neither the PR nor PD criteria. For responses other than PD, the combination treatment was repeated. Clinical visits, laboratory testing for blood counts, liver functionality, and tumor marker levels (CA19-9) were performed monthly.

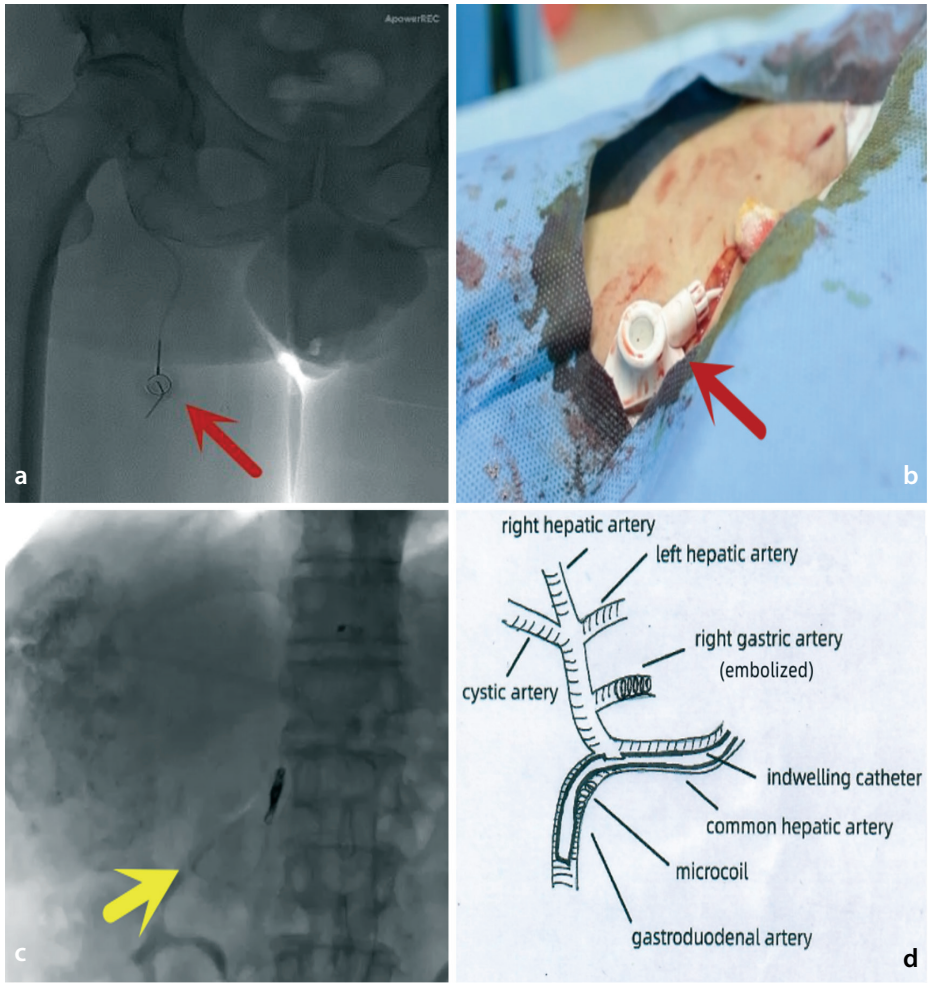

Figure 2. Intraoperative diagram of hepatic arterial infusion chemotherapy. The arterial port (Bard Access Systems, USA) is usually implanted subcutaneously 2 cm below the right groin of the patient, and the arterial catheter (**a** and **b**, red arrow) is then connected. The distal end of the arterial catheter is located in the gastroduodenal artery (**c**, yellow arrow). The distal hole of the arterial catheter is opened to allow the microcatheter into the gastroduodenum through the lateral hole, and the spring ring is implanted through the microcatheter to fix the arterial catheter into the gastroduodenal artery. The ductus arteriosus is compressed, and the chemotherapy drug flows to the internal hepatic artery through the lateral pore (if the right gastric artery is found, embolization is performed at the same time. D, schematic diagram).

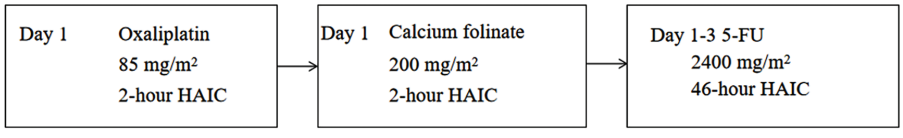

Figure 3. Schedule of chemotherapy administration. HAIC, hepatic arterial infusion chemotherapy.

Tolerability

Toxicity was evaluated according to the NCI-CTCAE guidelines. In the case of toxicity of grade 3 or above, treatment was temporarily suspended. Toxicity was evaluated every 2 or 3 days for each patient. After confirming that the toxicity had resolved to grade 1 or below, treatment was resumed with the same regimen. If toxicity of grade 3 or above was observed again after retreatment, treatment was temporarily suspended, and the patient resumed treatment at a reduced dose after the resolution was verified.

Statistical analysis

The statistical analyses were performed using SPSS 26.0 (IBM, Armonk, NY, USA). Continuous variables are expressed as the means and standard deviations or medians with ranges where appropriate. Qualitative variables are described as percentages or frequencies. The median progression-free survival (mPFS) and overall survival rate (OS %), objective response rate (ORR), disease control rate (DCR), and CR, PR, SD, and PD rates were also calculated.

Results

Baseline characteristics

The included patients' baseline characteristics are summarized in Table 1. Among the 28 patients, 10 had abdominal lymph node metastasis and 2 had portal vein tumor thrombus. All the patients were confirmed to have ICC through pathological examination. Of the 16 patients with abnormal CA 19-9 values, 12 (75%) exhibited a reduction from baseline. Additionally, 18 patients (64%) with an initial ECOG performance status >0 improved during therapy. Pain improved in 20 of the 28 initially symptomatic patients (71%).

Clinical outcomes of the combination therapy

The response and survival outcomes are summarized in Table 2. The mean number of treatment cycles for all participants was 6.4 cycles (range: 4–10 cycles). With regard to an

Table 1. The baseline characteristics of included patients

Characteristics		All patients (n = 28)
Age, year, median (range)		51.5 (28–62)
Gender (f/m)		14/14
PLT, × 10^9/L, median (range)		203 (89–449)
ECOG performance status		
0		0
1		24
2		4
WBC, × 10^9/L, median (range)		4.75 (2.33–13.1)
HB, g/L, median (range)		118 (74–155)
ALT, U/L, median (range)		55 (11–110)
AST, U/L, median (range)		44 (23–90)
TBIL, μmol/L, median (range)		17.5 (5.5–45.8)
ALB, g/L, median (range)		37.2 (26.5–41.9)
Child–Pugh class		
A		14
B		14
Portal vein tumor thrombus		2
Abdominal lymph node metastasis		10
Pretreatment		
TACE		5
PTCD		4
Systemic chemotherapy		19
CA 19-9 (U/mL)		
Baseline	≥1200	16
3 months later	<1200	12
Number of treatment cycles		6.4 (4–10)
Follow-up time (months)		11.3 (4–19)

PLT, platelet; ECOG: Eastern Cooperative Oncology Group; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; ALB, albumin; TACE, transcatheter arterial chemoembolization; PTCD: percutaneous transhepaticcholangial drainage.

Table 2. Tumor response

Responses	All patients (n = 28)
CR, n (%)	2 (7%)
PR, n (%)	14 (50%)
SD, n (%)	6 (21%)
PD, n (%)	6 (21%)
ORR, n (%)	16 (57%)
DCR, n (%)	22 (79%)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate.

early response, only two CRs were observed (Figure 4), and 14 and 6 patients achieved a PR and SD, respectively. However, six patients had PD. The ORR (CR + PR/all patients) and DCR (CR + PR + SD/all patients) were 57% and 79%, respectively.

The mPFS of the patients was 9.5 months (median follow-up time: 11.3 months; range: 4–19 months). The cumulative survival rate at 1 year was 83.3% (Figure 5). Four patients died of tumor progression.

Adverse effects

All patients were evaluated for adverse effects and complications related to the implantable port system. Port systems were successfully implanted in eight patients, with other patients receiving alternative methods. No complications were considered to be catheter-related toxicity. The adverse effects at initial treatment are summarized in Table 3. No treatment-related deaths occurred.

All 28 patients (100%) developed nausea and vomiting, but no severe cases of nausea or vomiting were observed. Twenty-four of the 28 (85.7%) patients developed abdominal pain, and two patients experienced severe abdominal pain after oxaliplatin injection. In these two patients, no significant improvement in symptoms was observed after lidocaine injection. Subsequently, when an intravenous infusion of butorphanol tartrate was used, the pain was significantly relieved. Mild diarrhea was observed in four patients (14.3%), and mild neurotoxicity was observed in two patients (7.1%).

Regarding blood toxicity, eight patients developed leukopenia, including two with grade 3 leukopenia. Moreover, 12 patients developed thrombocytopenia, including 2 with grade 3 thrombocytopenia. Severe blood toxicity complications in both of these patients were subsequently corrected through splenic artery embolization.

All patients were treated for at least four cycles. During the follow-up period, six patients discontinued treatment because of disease progression.

Discussion

Recent phase III clinical trials have demonstrated that treatment with GEMCIS in combination with durvalumab or pembrolizumab significantly improved OS compared with conventional chemotherapy alone with similar safety profiles in patients with unresectable or metastatic biliary tract cancers.[14,15] These studies have prompted further exploration of the triple combination treatment of HAIC, TKIs, and immune checkpoint inhibitors. In the present study, we demonstrated that the combination of HAIC, surufatinib, and toripalimab achieved promising patient survival (mPFS, 9.5 months; 1-year survival rate, 83.3%) as well as sufficient tumor response (ORR, 57%; DCR, 79%). In addition, the combination treatment-related adverse events were manageable.

Systemic chemotherapy can increase OS and improve the quality of life of patients with advanced ICC.[14] Several combination chemotherapy regimens have been investi-

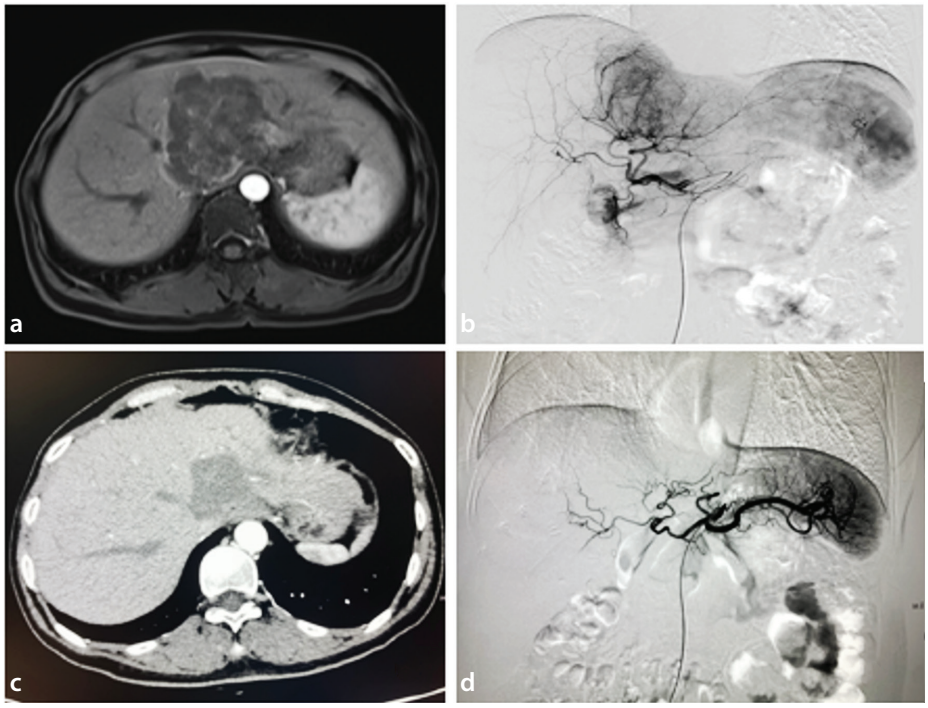

Figure 4. A 51-year-old female patient with ICC (confirmed through puncture biopsy). Magnetic resonance imaging revealed a large mixed density shadow in the liver (62 × 55 × 53 mm) (**a**). Digital subtraction angiography revealed an increased tortuous hepatic artery and obvious tumor staining (**b**). After three cycles of combination treatment, the computed tomography arterial phase demonstrated that the enhancement degree of the lesions was significantly reduced (**c**). Digital subtraction angiography indicated that the tumor staining had disappeared (**d**). ICC, intrahepatic cholangiocarcinoma.

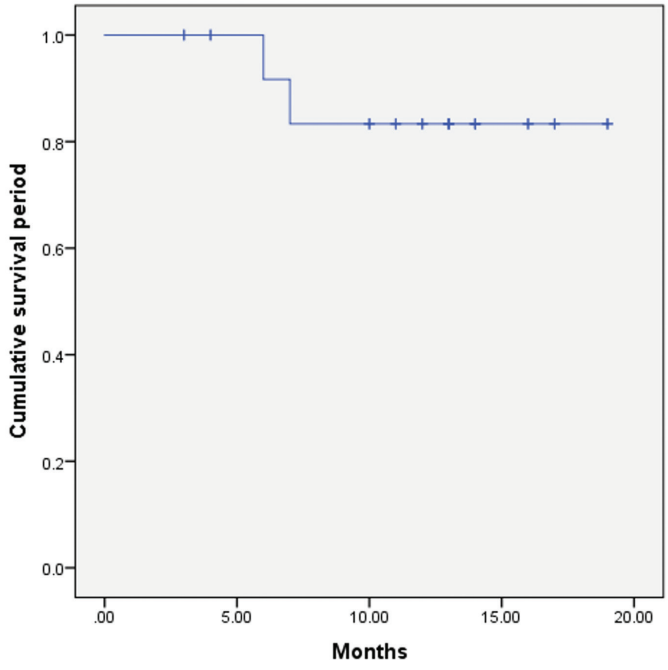

Figure 5. Kaplan–Meier curves illustrate the patient survival rates during the follow-up period.

gated, including gemcitabine/capecitabine, with an ORR of 25%, and gemcitabine/oxaliplatin, with an ORR of 50%.[14] A multicenter, open-label, phase 1 trial revealed that nivolumab (a PD-1 inhibitor) monotherapy had antitumor activity in Japanese patients with advanced cholangiocarcinoma, yielding an ORR of 3.3%, a median OS of 5.2 months, and an mPFS of 1.4 months. However, the combination therapy with nivolumab and chemotherapy achieved improved survival benefits in terms of a higher ORR (33.3%), longer median OS (15.4 months), and longer mPFS (4.2 months).[16] The multicenter, global, phase-3 TOPAZ-1 trial reported that GEMCIS chemotherapy plus durvalumab could significantly increase the median OS by 1.3 months (median OS: 12.8 vs. 11.5 months) when used as the first-line treatment for unresectable and metastatic cholangiocarcinoma compared with GEMCIS chemotherapy alone. In another study, the ORR was 26.7% in a GEMCIS chemotherapy plus durvalumab group, which surpassed that in the GEMCIS chemotherapy group.[17] Systemic chemotherapy has only limited benefits. The median OS after GEMCIS therapy is still <1 year.[18,19] Some studies have evaluated the use of cisplatin in combination with a bolus of 5-FU and epirubicin, with tumor ORRs ranging from 10% to 35% and a median OS of 11 months.[10,20] Another study by Valle et al.[3] reported a median OS of 11.7 months from the ABC-02 trial, and this was also reported in a study by Fu et al.[21] These rates were higher in our study than in previous studies. However, Shi et al.[10] reported on the efficacy of toripalimab combined with lenvatinib and GEMOX as first-line therapy for advanced ICC. The median OS and PFS were 22.5 and 10.2 months, respectively. Our data demonstrated a similar clinical application prospect (mPFS of 9.5 months, and the cumulative survival rate from the time of diagnosis was 83.3% at 1 year. The rationale for the use of HAIC can be summarized as follows. First, ICCs are usually confined to the liver, and patients mainly die of liver failure. Second, some drugs result in high hepatic extraction after the first pass. Moreover, the blood supplied to the upper biliary tree and gallbladder is derived from the hepatic artery.[17,22] The administration of oxaliplatin through the hepatic artery provides a high drug concentration in the perfused blood, and systemic complications are much lower.[23]

Few studies have focused on systemic ICC treatments, and most of these studies did not yield clear results. Therefore, it is difficult to draw a conclusion about which is preferable for systemic or locoregional therapies. Moreover, limited data related to maintenance therapy for ICC are available. For this reason, the present study adopted toripalimab and surufatinib maintenance therapy, and innovative data for the treatment method were reported.

Toripalimab is a humanized anti-PD-1 IgG4 monoclonal antibody approved for clinical trials by the US Food and Drug Administration (FDA) and China's National Medical Products Administration. This drug has demonstrated promising efficacy and safety profiles for use in treating urologic cancer, melanoma, and gastric cancer.[21,24-26]

Table 3. Adverse events

Events	All patients (n = 28)	
	Any grade	Grade 3 to 4
Nausea and vomiting	28	0
Abdominal pain	24	2
Diarrhea	4	0
Neurotoxicity	2	0
Leukopenia	8	2
Thrombopenia	12	2
Mucositis	0	0
Infection	0	0

Surufatinib is a multikinase inhibitor that targets VEGF receptors 1 to 3, FGFR 1, and colony-stimulating factor 1 receptors. A high expression level of VEGF was detected in 53.8% of ICCs and was considered to be involved in hematogenous metastasis. The FGFR signaling pathway is also abnormally activated in ICC and is associated with an unfavorable prognosis.[27,28] Finally, considering that surufatinib and chemotherapy regimens can significantly upregulate PD-L1 expression, using these therapies with anti-PD-1 treatment may significantly enhance their effects. Notably, combined therapy with an anti-PD-1 antibody and surufatinib has been reported to be useful for the treatment of several cancer types, and the FDA has approved the combination of surufatinib and toripalimab for treating advanced endometrial cancer and advanced renal cell carcinoma.

Maintenance therapy cannot be performed in unfit patients who are not clinically indicated for chemotherapy. For this reason, maintenance therapy is usually performed only in those who respond to HAIC, primarily to prolong the benefits of HAIC on survival. Maintenance therapy has demonstrated promising results in terms of tumor response, survival, and progression delay in many types of cancers. These results may suggest a possible advantage of maintenance therapy for ICC. Therefore, combining anti-PD-1 therapy with the combination of surufatinib and HAIC for the treatment of ICC seems reasonable. Our findings suggest that HAIC combined with toripalimab and surufatinib may be a new and promising treatment approach for advanced ICC.

The present study has certain limitations that must be considered. The main limitation of this study is that it is retrospective, and the number of participants was relatively limited. A technical limitation is that polymerase chain reaction and DNA sequencing have not yet been performed to detect antimicrobial resistance genes, whose characterization is also essential for surveillance, infection control, and therapeutic purposes. In additional studies, we will perform genome-wide sequencing to identify a pathogen by comparing its sequence to a database of known pathogens to determine its closest relatives.

In conclusion, future randomized controlled studies are needed to enhance the reliability of the findings because of the short follow-up duration. Finally, as previously mentioned, the sample size should be increased to obtain more conclusive results.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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