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Selective Internal Radiation Therapy with Yttrium-90 Resin Microspheres Followed by Gemcitabine plus Cisplatin for Unresectable Intrahepatic Cholangiocarcinoma: A Phase 2 Single-Arm Multicenter Clinical Trial

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Keywords
Liver neoplasms · Bile duct cancer · Radiotherapy · Chemotherapy · Combination

Abstract

Introduction: This investigator-initiated clinical trial aims to study the efficacy and safety of administering selective internal radiation therapy with resin yttrium-90 microspheres (SIRT) followed by standard chemotherapy in unresectable intrahepatic cholangiocarcinoma (ICC). ***Methods:*** A phase 2 single-arm multicenter study was conducted in patients with unresectable ICC (NCT02167711). SIRT was administered at dose of 120 Gy targeted at tumor followed by commencement of gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 on days one and eight of a 21-day cycle. The primary endpoint was overall survival (OS), and the secondary endpoints include progression-free survival (PFS), response rate according to Response Evaluation Criteria in solid tumors 1.1, toxicity, and time from SIRT to commencement of chemotherapy. ***Results:*** Total 31 patients were screened and twenty-four were recruited. All patients completed SIRT and

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16 of them underwent subsequent chemotherapy. The median cycle of chemotherapy was 5 (range: 1–8). The median OS was 13.6 months (95% CI: 5.4–21.6) for the intent-to-treat population. Among 16 patients undergoing chemotherapy, the median OS was 21.6 months (95% CI: 7.3–25.2) and the median PFS was 9 months (95% CI: 3.2–13.1). The response rate was 25% (95% CI: 3.8–46.2%), and the disease control rate was 75% (95% CI: 53.8–96.2%). No new safety signal was observed, with fewer than 10% of patients suffering from grade 3 or higher treatment-related adverse events. The median time from SIRT to chemotherapy was 29 (range: 7–42) days. Eight patients could not receive chemotherapy due to rapid progressive disease ($n = 4$), underlying treatment unrelated comorbidities ($n = 2$), and withdrawal of consent due to personal reasons ($n = 2$). ***Conclusions:*** Treatment of SIRT followed by standard gemcitabine and cisplatin chemotherapy is feasible and effective for unresectable ICC. Further studies are required to study the optimal sequence of SIRT and chemotherapy.

Introduction

Biliary tract cancer accounts for 3% of all gastrointestinal malignancies [1]. The annual incidence of cholangiocarcinoma in western countries is approximately 2 per 100,000 individuals, and the incidence ranges widely from 3.9 to over 100 per 100,000 in Asian countries. The incidence of intrahepatic cholangiocarcinoma (ICC) is rising globally, while the incidence of its extrahepatic counterpart is reducing worldwide [2, 3]. For inoperable ICC, a chemotherapy regimen of gemcitabine plus cisplatin (Gem-Cis) is the standard treatment as shown by the phase 3 clinical trial, which demonstrated that Gem-Cis is associated with better overall survival (OS) than gemcitabine alone in patients with advanced biliary tract cancer [4].

Locoregional treatment such as transarterial chemoembolization (TACE) or selective internal radiation therapy with yttrium-90 (SIRT) has been investigated for locally advanced ICC [5]. A retrospective study reported an improvement of OS from 5.7 months to 11.7 months among patients with ICC treated with drug eluting-based TACE using beads containing irinotecan than conventional TACE with mitomycin C [6]. For SIRT, a retrospective study reported a median OS of 22 months in ICC [7]. Several other early phase clinical trials demonstrated radiological response rates (RRs) ranging from 11% to 36% with the use of SIRT for unresectable ICC [8, 9]. Therefore, SIRT is considered by clinicians to be one of the treatment options for inoperable ICC with main disease burden confined to the liver [10].

To enhance the treatment efficacy for ICC, SIRT could theoretically be combined with the standard Gem-Cis chemotherapy. There are two ways of combining SIRT with chemotherapy: one approach is to administer SIRT after or during the administration of systemic chemotherapy, which could maximize the synergism between SIRT and systemic chemotherapy but may be associated with higher rate of toxicity. Another approach is to administer SIRT prior to commencement of chemotherapy, which could potentially enhance local control of ICC, especially for locally advanced disease, prior to systemic control. The results of the former approach have recently been shown in a phase II MISPHEC trial in Europe which reported a high RR of 39% (90% CI: 26–53%) at 3 months and an acceptable safety profile without cirrhosis was seen among forty-one western patients [11]. To study the latter approach, an investigator-initiated clinical trial was commenced by oncology centers in Hong Kong, Singapore, and Thailand to study the efficacy and safety of administration of SIRT followed by Gem-Cis in unresectable ICC. Results presented in this manuscript will provide further clinical evidence on the treatment effectiveness in our population.

Materials and Methods

Study Design

This is an open-label, single-arm, multicentered, and investigator-initiated phase 2 clinical trial (NCT02167711) conducted from October 2014 to December 2020. Four oncology centers from Hong Kong (the Prince of Wales Hospital, The Chinese University of Hong Kong), Singapore (the National Cancer Centre Singapore and the National University of Singapore), and Thailand (the Chulabhorn Hospital, Bangkok) participated in this study. This clinical trial was approved by the respective ethics committees of all participating institutes and was conducted in accordance with the International Conference on Harmonization-Good Clinical Practice and the Declaration of Helsinki.

Patients

All study participants provided written informed consent before enrollment to the study. Key inclusion criteria were patients aged 18 years or older; histologically or cytologically confirmed ICC; disease not amenable to surgery; predominant disease load in the liver; naïve to locoregional or systemic treatment; Eastern Cooperative Oncology Group Performance Status 0 or 1; presence of at least one measurable disease lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; adequate hematological, renal, and hepatic functions (platelet count $\geq 100 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, bilirubin ≤ 30 μmol/L, al-

bumin ≥30 g/L, alanine transaminase ≤3 × institutional upper limit of normal [ULN], international normalized ratio ≤1.5, serum creatinine ≤1.5 × ULN). Key exclusion criteria included the presence of extrahepatic disease other than lymph node disease; biliary obstruction with no possibility of drainage; prior treatment of chemotherapy for the cholangiocarcinoma; prior radiation therapy to the upper abdomen; complete thrombosis of the main portal vein; and tumor volume of more than 50% of the total liver volume.

Study Treatment

All patients scheduled to receive one course of SIRT at a dose of at least 120 Gy to the intrahepatic tumor, and the final dose of yttrium-90 resin microspheres was calculated on the basis of partition model [12, 13]. In brief, prior to the administration of SIRT, patients were required to demonstrate a lung shunting ≤15% and a tumor-to-normal ratio higher than 2 as determined by gamma camera imaging of technetium-99m macroaggregated albumin. The procedures of SIRT were administered at a lobar level for unilobar disease or at whole-liver level for bilobar disease. Radiation dose ranged from 1.9 to 4.4 GBq to achieve a tumor-absorbed dose of 120 Gy or more. In cases with bilobar disease or centrally located tumors, SIRT was delivered in one treatment session through either catheterization of the proper hepatic artery with embolization of the right gastric artery or sequential catheterization of the right and left hepatic artery. Patients were assessed for any acute toxicity related to SIRT 4 weeks after the SIRT treatment. Patients with grade 1 or less treatment-related toxicities and adequate hematological, renal, and hepatic functions were scheduled to commence Gem-Cis chemotherapy. After recruitment of 10 patients, the protocol was amended to allow the assessment and commencement of chemotherapy as early as 1 week after SIRT because of absence of alarming safety concerns. A maximum of eight cycles of chemotherapy with cisplatin at a dosage of 25 mg/m^2 on days one and eight, followed by the 3-weekly administration of gemcitabine at 1,000 mg/m^2 on day one and eight [4].

Assessment

The primary endpoint was OS which was defined as the time from commencement of study treatment to the date of death from any cause. The secondary endpoints were progression-free survival (PFS), RR, disease control rate (DCR), toxicity, and the duration from SIRT to the commencement of chemotherapy. PFS was defined as the time from start of study treatment to the first documentation of objective tumor progression or to death from any cause. RR was defined as the proportion of patients with confirmed complete response or confirmed partial response according to RECIST v1.1, relative to the total evaluable patient population. DCR was defined as the proportion of patients with confirmed complete response, partial response, or stable disease for at least 12 weeks of study according to the RECIST. Computed tomography scan was performed every 6 weeks until documentation of progressive disease (PD) according to RECIST v1.1. Patients who developed PD were managed according to institutional treatment practice for second-line chemotherapy or best supportive care. For patients who have stopped chemotherapy for any reasons other than withdrawal of consent, regular follow-up visit was arranged to monitor any delayed toxicity till 9 months after SIRT. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria v4·0 Adverse Event Classification. To study any delayed treatment-related toxicity, all adverse events were documented till 9 months from the time of SIRT treatment.

Statistical Analysis

Kaplan-Meier analysis was conducted to evaluate OS and PFS. The RR and DCR were reported as rates along with the corresponding 95% confidence interval (CI) using standard methods based on the binomial distribution. The rate and severity of toxicities as well as demographic data were summarized by descriptive statistics. The hazard ratio and corresponding 95% CI were computed. The SAS® Software version 9.4 (SAS Institute, Cary, NC, USA) were used for analyses. For sample size justification, based on a previous prospective study, the median OS of advanced cholangiocarcinoma was approximately 10 months [4]. It was hypothesized that the addition of SIRT to Gem-Cis could improve the median OS to 14 months. To detect the survival difference of 4 months with one-sided alpha level of 5% and a power of 80%, a recruitment of 24 patients was required for this clinical trial.

Results

Patients

Between October 2014 and April 2020, a total of 31 patients underwent screening for the study; 7 patients had screening failure with reasons including technetium-99m macroaggregated albumin scan showing ineligibility for SIRT (2 patients had low tumor-liver ratio; 1 patient had high lung shunting), rapid PD during screening (1 patient), acute stroke (1 patient), worsening liver function during screening (2 patients). Finally, 24 with unresectable ICC were enrolled in the study. Among 24 patients (intent-to-treat population), 15 (62.5%) patients were male with a median age of 62 years (range: 35–79). Four patients were hepatitis B surface antigen-positive, while none of them tested positive for anti-hepatitis C virus. Three-fourth of the patients had stage IVA/IVB disease according to the AJCC TNM staging seventh edition [14]. The median diameter of the largest tumor was 7.4 cm (range: 1.4–14.0 cm). The baseline characteristics of patients are listed in Table 1.

Efficacy

All patients were treated with SIRT according to the protocol and sixteen (67%) received subsequent Gem-Cis chemotherapy with a median of 5.0 cycles (range: 1–8). The median time from completion of SIRT to the commencement of Gem-Cis was 29 days (range: 7–42 days). Eight patients were unable to receive subsequent chemotherapy due to disease progression resulting in worsening performance status (n = 4, 16.5%), withdrawal of consent (n = 2, 8%), and poor underlying medical conditions (n = 2, 8%; one due to the presence of liver abscess and one due to inadequate renal function before commencement of chemotherapy).

Table 1. Baseline characteristics of patients (*N* = 24)

Characteristics	*n* (%) or median (range)
Age, years	
Median (range)	62 (35–79)
Sex (male:female), *n* (% of patients)	15 (62.5):9 (37.5)
ECOG Performance Status, *n* (% of patients)	
0	21 (87.5)
1	3 (12.5)
Tumor stage, *n* (% of patients)	
T1	2 (8.3)
T2	14 (29.2)
T3	5 (20.8)
T4	1 (4.2)
Unknown	2 (8.3)
Node stage, *n* (% of patients)	
N0	8 (33.3)
N1	9 (37.5)
Nx	7 (29.2)
Metastasis stage, *n* (% of patients)	
M0	15 (62.5)
M1	9 (27.5)
Tumor stage (AJCC TNM 7th edition)	
I	1 (4.2)
II	1 (4.2)
III	4 (16.6)
IVA	12 (50.0)
IVB	6 (25.0)
Tumor diameter of largest tumor, cm, median (range)	7.4 (1.4–14.0)
HBsAg-positive	4 (16.7)
Anti-HCV-positive	0 (0)
ALBI	
Grade 1	17 (70.8)
Grade 2	7 (29.2)
Laboratory parameters, median (range)	
Hemoglobin, g/dL	12.8 (10.0–15.0)
White blood cells, $\times 10^9$/L	6.6 (4.3–17.2)
Neutrophils, $\times 10^9$/L	4.4 (2.4–14.5)
Platelet, $\times 10^9$/L	233 (108–395)
Bilirubin, μmol/L	10 (0.4–29.4)
Albumin, g/L	40.5 (25–47)
Alkaline phosphatase, IU/L	152.5 (66–485)
Alanine aminotransferase, IU/L	25.5 (8–139)
Location, *n* (% of patients)	
Hong Kong	7 (28.2)
Singapore	6 (25.0)
Thailand	11 (45.8)

AJCC TNM, American Joint Committee on Cancer Tumor Node Metastases; ALBI, Albumin-Bilirubin; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

In the intent-to-treat population (i.e., patients receiving at least one cycle of SIRT regardless of receiving chemotherapy or not; *n* = 24), the overall RR was 16.7% (95% CI: 1.8–31.6%) and the DCR was 58.3% (95% CI: 38.6–78.1%). Among 16 patients who received at least one cycle of Gem-Cis chemotherapy following SIRT, the overall RR was 25% (95% CI: 3.8–46.2%) and the DCR was 75% (95% CI: 53.8–96.2%). Respective waterfall plot is shown in Figure 1. There was no downstaging of tumors to surgery seen in the study population. After a median follow-up of 8.5 months (range: 1.1–30.0 months), 19 patients died among which seventeen had disease progression. For the intent-to-treat population (*n* = 24), the median PFS was 6.6 months (95% CI: 2.5–9.8 months) (shown in Fig. 2) and the median OS was 13.6 months (95% CI: 5.4–21.6 months) (shown in Fig. 3). For those who also received at least one cycle of subsequent Gem-Cis chemotherapy, the media PFS was 9.0 months (95% CI: 3.2–13.1 months) (shown in online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525489) and the median OS was 21.6 months (95% CI: 7.3–25.2 months) (shown in online suppl. Fig. 2).

Safety

The profile and rate of treatment-related toxicity are listed in Table 2, and the respective toxicity and toxicity related to SIRT or Gem-Cis chemotherapy are listed in online supplementary Table 1. In summary, lower than 10% of the intent-to-treat population had treatment-related grade 3–4 toxicities. During the treatment phase of SIRT, grade 3–4 toxicities included gastrointestinal disorders such as abdominal pain (*n* = 1, 4%), vomiting (*n* = 1, 4%), ascites (*n* = 1, 4%), and abnormal blood tests such as elevated AST (*n* = 1, 4%), increased blood bilirubin (*n* = 1, 4%), and hypercalcemia (*n* = 1, 4%). During the phase of subsequent Gem-Cis chemotherapy, common grade 3–4 toxicities were mainly marrow suppression: neutropenia (*n* = 4, 17%), anemia (*n* = 2, 8%), and thrombocytopenia (*n* = 2, 8%). Other grade 3–4 toxicities were hyponatremia (*n* = 2, 8%), abdominal pain (*n* = 2, 8%), and vomiting (*n* = 2, 8%), respectively. The median time from SIRT to commencement of Gem-Cis chemotherapy was 29 days (range: 7–42 days).

Discussion/Conclusion

This is the first clinical trial studying the serial combination of SIRT followed by standard Gem-Cis chemotherapy in the ICC population. The current clinical trial

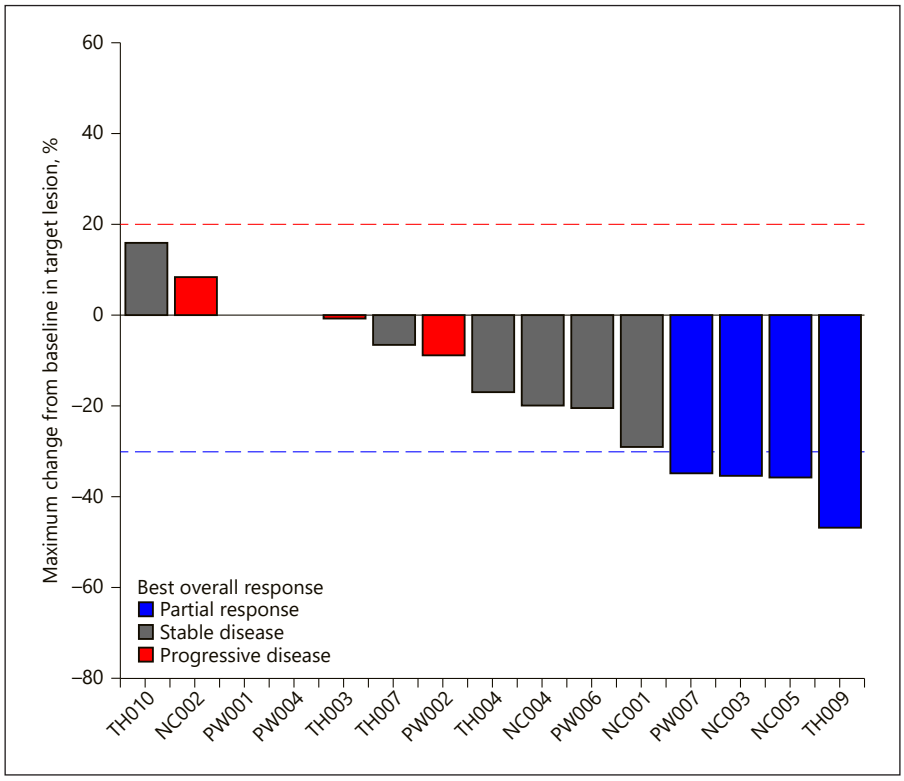

Fig. 1. Waterfall plot showing maximum changes in tumor size of target lesions.

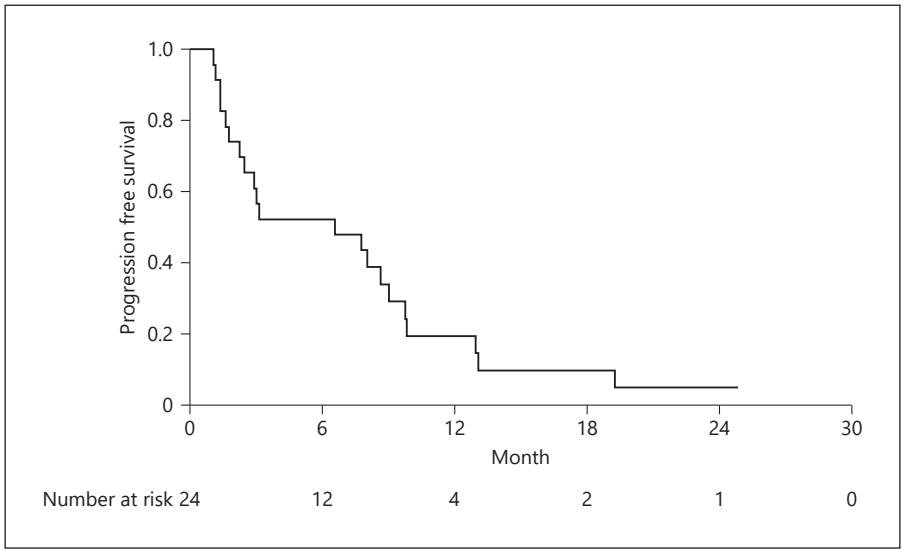

Fig. 2. Kaplan-Meier curve of the PFS in the intent-to-treat population (n = 24).

reports a median OS of 13.6 months in the intent-to-treat population, which is close to 14 months as hypothesized in the predefined statistical assumption. Additionally, more remarkable benefits are observed among the 16 patients who could proceed to Gem-Cis chemotherapy with a median OS of over 21 months and median PFS of 9 months. Distinct from other biliary tract cancers, ICC is amenable to liver-directed locoregional treatment. The current study suggests that a serial addition of locoregional therapy, in the form of SIRT, could potentially offer synergistic benefits with systemic treatment in patients with unresectable ICC with main disease burden in the liver.

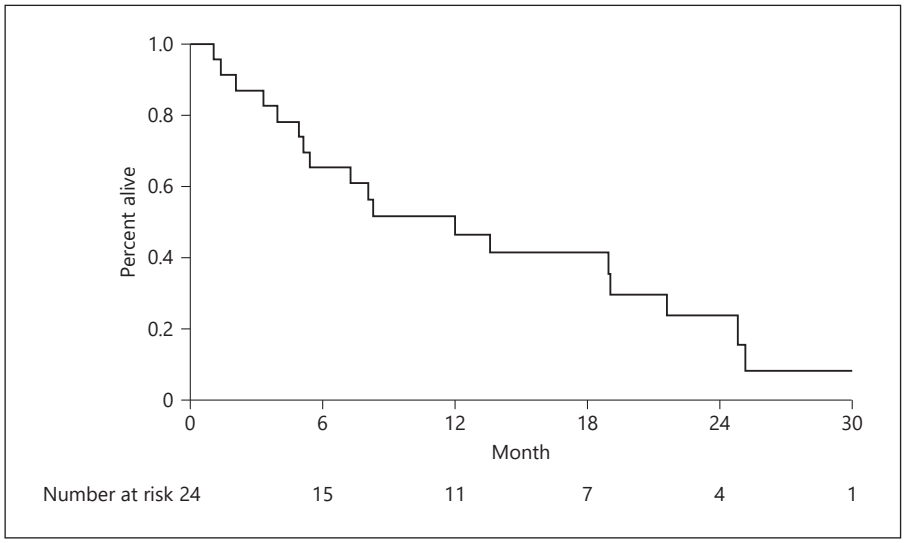

Fig. 3. Kaplan-Meier curve of the OS in the intent-to-treat population (n = 24).

Regarding treatment-related toxicity, no new safety signals are observed in the study population. In this study, grade 3 and 4 SIRT-related adverse events occurred in fewer than 10% of patients. Two reasons may contribute to the low toxicity rate seen with SIRT in this clinical trial. First, during the planning of SIRT, it is possible that we mandated lung shunting at a lower cut-off of 15%, instead of 20%, which may prevent radiation-induced lung injury. Second, all four participating centers of this clinical trial have extensive experiences in the administration of SIRT to hepatocellular carcinoma. For chemotherapy toxicity, our figures were generally lower than that reported in the UKABC-02 study largely because we focused on treatment-related toxicity. Also, patients experiencing toxicity after SIRT were prohibited from receiving chemotherapy until severity of adverse event was reduced to grade 1 or resolved completely. The initial design of the study required a 4-week window period after SIRT due to concerns about recall phenomena related to gemcitabine immediately after radiotherapy. However, after the first 10 patients were recruited, it was found that no recall-related toxicity was observed in patients undergoing chemotherapy. The protocol was therefore amended from a 4-week window to a minimal 1-week window period for commencement of chemotherapy after SIRT. Finally, in our study, the median time between SIRT and chemotherapy was 29 days.

We observed that 8 patients were unable to proceed to chemotherapy after SIRT due to PD in 4 patients. Among those 4 patients, three had progression of intrahepatic tumor and one had development of extrahepatic disease. In those 4 patients, PD was associated with rapidly deteriorating performance status, suggestive an aggressive biology of ICC in some patients with biliary tract cancer. Another possible reason is due to delayed administration of chemotherapy in this group of advanced disease. To prevent early progression, future studies should evaluate whether an upfront administration of chemotherapy prior to SIRT could prevent early aggressive progression. Another 2 patients developed medical condition, namely liver abscess and impaired renal function, which precluded them from receiving chemotherapy. Detailed review of medical records revealed that both patients had comorbidities, including recurrent pyogenic cholangitis and diabetes-related renal impairment, respectively, prior to the recruitment to the clinical trial. Those comorbidities had fluctuating disease courses; hence, they did not fulfill exclusion criteria at the time of enrollment. Finally, another 2 patients withdrew from the study due to personal reasons which were not related to treatment procedures. Above patterns of failure could provide references to future design of clinical trials on the combination of SIRT and chemotherapy.

During the conduct of the current study, another phase II MISPHEC clinical trial has been published on the combination of SIRT and chemotherapy for ICC [11]. In this study, it was found that the radiologic RR was 41% (17 out of 41 evaluable patients) according to RECIST, and the median PFS and OS were 14 and 22 months, respectively. Further, twenty-two of them could have downstaging of disease to surgery. In comparison, the efficacy results observed in our study were less favorable. Multiple reasons may explain these differences: first, our study population was composed of more patients with ad-

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Table 2. All treatment-related adverse events*

Category	AE	Grade 0	%	Grade 1	%	Grade 2	%	Grade 3	%	Grade 4	%
Investigations	Neutrophil count decreased	13	54	2	8	5	21	2	8	2	8
Investigations	Platelet count decreased	15	63	6	25	1	4	2	8	0	0
Gastrointestinal disorders	Abdominal pain	16	67	3	13	3	13	2	8	0	0
Blood and lymphatic system disorders	Anemia	20	83	1	4	1	4	2	8	0	0
Gastrointestinal disorders	Vomiting	20	83	2	8	0	0	2	8	0	0
Investigations	Aspartate aminotransferase increased	21	88	0	0	1	4	2	8	0	0
Metabolism and nutrition disorders	Hyponatremia	21	88	1	4	0	0	1	4	1	4
Investigations	Blood bilirubin increased	22	92	0	0	0	0	1	4	1	4
Infections and infestations	Sepsis	22	92	0	0	0	0	0	0	2	8
Gastrointestinal disorders	Gastrointestinal disorders – other	20	83	3	13	0	0	1	4	0	0
Gastrointestinal disorders	Nausea	20	83	3	13	0	0	1	4	0	0
Investigations	Alanine aminotransferase increased	22	92	1	4	0	0	1	4	0	0
Investigations	Alkaline phosphatase increased	22	92	1	4	0	0	0	0	1	4
Gastrointestinal disorders	Ascites	22	92	1	4	0	0	1	4	0	0
Gastrointestinal disorders	Gastric ulcer	23	96	0	0	0	0	1	4	0	0
Metabolism and nutrition disorders	Hypercalcemia	23	96	0	0	0	0	0	0	1	4
Investigations	White blood cell decreased	23	96	0	0	0	0	1	4	0	0
General disorders and administration site conditions	Fatigue	17	71	5	21	2	8	0	0	0	0
General disorders and administration site conditions	Fever	18	75	6	25	0	0	0	0	0	0
Metabolism and nutrition disorders	Hypoalbuminemia	21	88	1	4	2	8	0	0	0	0
Metabolism and nutrition disorders	Hypokalemia	21	88	3	13	0	0	0	0	0	0

* The above AEs were listed in order according to rate of grade 3–4 events; only AEs of higher than 10% (all grades) or 4% (grades 3–4) are listed.

vanced disease, including 75% of patients with evidence of extrahepatic disease in either regional lymph nodes (25% of the whole population) or distant lymph nodes (50% of the whole population). In contrast, 58% of patients in the MISPHEC study belonged to locally advanced disease without extrahepatic disease (except hilar lymph nodes) [11]. Second, the MISPHEC study adopted a different treatment protocol with commencement of Gem-Cis chemotherapy first, with SIRT performed during cycle one of chemotherapy [11]. Additional SIRT may be given from cycle three of chemotherapy in case of bilobed liver involvement or anatomic variants of liver arteries. In our current study, patients received less aggressive treatment with only one cycle of SIRT. Third, the oncologic and surgical practices may be different between Eastern and Western centers. For example, experiences on hepatocellular carcinoma suggested that Asian surgeons tend to adopt more aggressive surgical approaches which may render patients with more advanced disease to be treated with nonsurgical treatment [15]. Overall, both studies consistently demonstrated the incorporation of SIRT to standard Gem-Cis chemotherapy could improve the outcomes of patients with advanced ICC.

There are few limitations in the current study. First, only Asian patients were recruited; hence, the data may not be generalizable to non-Asian populations. While there are genomic differences between Eastern and Western patients with ICC, it is unclear whether the treatment outcomes differ significantly between the two populations [16]. Second, a lack of control arm in the current study may limit the interpretation of survival outcomes of the experimental arm. During the design of this study, the primary objective was to generate early data to look for signal of synergism of the combinational treatment. A randomized study on the use of SIRT followed by Gem-Cis chemotherapy compared to Gem-Cis chemotherapy alone in patients with unresectable ICC (NCT02807181) was previously initiated but was unfortunately terminated due to slow accrual. Third, recent data on recently reported predictive biomarkers in cholangiocarcinoma such as the fibroblast growth factor receptor 2 or isocitrate dehydrogenases were not available in the current clinical trial [17]. As a result, there are no analyses on those tissue biomarkers in relevance to SIRT-chemotherapy combination.

In conclusion, the current phase 2 clinical trial shows that the addition of SIRT to Gem-Cis chemotherapy is potentially effective and safe in unresectable ICC. Further studies are indicated to study the optimal timing of SIRT administration to chemotherapy backbone.

Acknowledgment

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Statement of Ethics

This study protocol was reviewed and approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee in Hong Kong (approval no.: 2014.091-T), Human Research Ethics Committee Chulabhorn Research Institute in Thailand (approval no.: 021/2558), and SINGHEALTH Centralised Institutional Review Board in Singapore (approval no.: 2014/2023). Written informed consent was obtained from participants to participate in this study. This clinical trial was approved by the respective ethics committees of all participating institutes and was conducted in accordance with the International Conference on Harmonization-Good Clinical Practice and the Declaration of Helsinki. The clinical trial number is NCT02167711.

Conflict of Interest Statement

Stephen Lam Chan served as advisor for Astra-Zeneca, MSD, Eisai, and Ipsen and received research funding from Bayer, Eisai, Ipsen, SIRTEX, and MSD. Su Pin Choo has consulted for or received honorariums/fees from Astra-Zeneca, MSD, Eisai, Ipsen, BMS, Bayer, and Roche. David Tai has consulted for or received honorariums/fees from Novartis, MSD, Ipsen, Eisai, and BMS. Raghav Sundar has received honoraria from Bristol-Myers Squibb, Lilly, and MSD; has advisory activity with Bristol-Myers Squibb, Eisai, and AstraZeneca; received research funding from Paxman Coolers; and has received travel grants from AstraZeneca, Roche, and Taiho Pharmaceutical. All not related to submitted works. David C.E. Ng received funding from Sirtex, Bayer, MSD, and Novartis. Kelvin S.H. Loke has received honoraria from SIRTEX. Wei Peng Yong has consulted for or received honorariums/fees from Abbvie, Amgen, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Novartis, MSD, Sanofi, and Taiho. Other authors have no conflicts of interest to declare.

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Author Contributions

Concept and design: Stephen Lam Chan and Simon Yu. Recruitment and management of patients and approval of final manuscript: Stephen Lam Chan, Chanisa Chotipanich, Su Pin Choo, Su Wen Kwang, Frankie Mo, Akeanong Worakitsitisatorn, David

Tai, Raghav Sundar, David C.E. Ng, Kelvin S.H. Loke, Leung Li, Kelvin K. Ng, Wei Peng Yong, and Simon Yu. Statistical analysis: Stephen Lam Chan and Frankie Mo. Drafting of manuscript: Stephen Lam Chan, Chanisa Chotipanich, Frankie Mo, and Simon Yu.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to both corresponding authors.

References

1 Patel N, Benipal B. Incidence of cholangiocarcinoma in the USA from 2001 to 2015: a US Cancer Statistics analysis of 50 states. Cureus. 2019;11(1):e3962.
2 Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. Lancet. 2021;397(10272):428–44.
3 Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, et al. Expert consensus document: cholangiocarcinoma – current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol. 2016;13(5):261–80.
4 Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81.
5 Edeline J, Lamarca A, McNamara MG, Jacobs T, Hubner RA, Palmer D, et al. Locoregional therapies in patients with intrahepatic cholangiocarcinoma: a systematic review and pooled analysis. Cancer Treat Rev. 2021;99:102258.
6 Kuhlmann JB, Euringer W, Spangenberg HC, Breidert M, Blum HE, Harder J, et al. Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. Eur J Gastroenterol Hepatol. 2012;24(4):437–43.
7 Hoffmann RT, Paprottka PM, Schön A, Bamberg F, Haug A, Dürr EM, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. Cardiovasc Intervent Radiol. 2012;35(1):105–16.
8 Saxena A, Bester L, Chua TC, Chu FC, Morris DL. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. Ann Surg Oncol. 2010;17(2):484–91.
9 Rafi S, Piduru SM, El-Rayes B, Kauh JS, Kooby DA, Sarmiento JM, et al. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. Cardiovasc Intervent Radiol. 2013;36(2):440–8.
10 Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. HPB. 2015;17(8):669–80.
11 Edeline J, Touchefeu Y, Guiu B, Farge O, Tougeron D, Baumgaertner I, et al. Radioembolization plus chemotherapy for first-line treatment of locally advanced intrahepatic cholangiocarcinoma: a phase 2 clinical trial. JAMA Oncol. 2020;6(1):51–9.
12 Lau WY, Leung WT, Ho S, Leung NW, Chan M, Lin J, et al. Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. Br J Cancer. 1994;70(5):994–9.
13 Salem R, Padia SA, Lam M, Bell J, Chiesa C, Fowers K, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging. 2019;46(8):1695–704.
14 Edge SB, Compton C, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
15 Choo SP, Tan WL, Goh BKP, Tai WM, Zhu AX. Comparison of hepatocellular carcinoma in Eastern versus Western populations. Cancer. 2016;122(22):3430–46.
16 Cao JY, Hu J, Liu SQ, Meric-Bernstam F, Abdel-Wahab R, Xu JJ, et al. Intrahepatic cholangiocarcinoma: genomic heterogeneity between Eastern and Western patients. JCO Precis Oncol. 2020;4:557–69.
17 Lamarca A, Barriuso J, McNamara MG, Valle JW. Molecular targeted therapies: ready for "prime time" in biliary tract cancer. J Hepatol. 2020;73(1):170–85.