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Original Article

A combination of locoregional treatment with systemic therapy after atezolizumab plus bevacizumab failure for unresectable hepatocellular carcinoma provides survival benefit

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Abstract: Atezolizumab plus bevacizumab (A+B) is used to treat unresectable hepatocellular carcinoma (HCC), but the optimal rescue therapy after A+B remains unclear. Combining locoregional therapy (LRT) with systemic treatment has been shown to improve tumor control, but the role in patients who fail A+B is unknown. We retrospectively enrolled patients who experienced radiological progression after A+B. Objective response rate (ORR), disease control rate (DCR), post progression survival (PPS), and secondary progression-free survival (PFS) were evaluated by modified RECIST. Inverse probability weighting (IPW) was used to balance baseline clinical features. A total of 61 patients were enrolled with a median age of 60.7 years, 83.6% male, 88.5% viral hepatitis-related, and 60.7% without prior systemic treatment before A+B. Patients receiving sequential therapies had significantly longer PPS than supportive care (10.5 vs. 2.3 months, P<0.0001). Among 37 patients received sequential systemic treatment, 18 received combined LRT. The median follow-up after post A+B failure was 6.6 months. The combined LRT group had higher ORR (27.8 vs. 0%, P=0.0197) and DCR (72.2 vs. 26.3%, P=0.0052) than systemic alone group. The median PPS and secondary PFS were significantly longer in combined LRT group (PPS: 12.2 vs. 5.8 months, P=0.0070; PFS: 5.0 vs. 2.6 months, P=0.0134) than systemic alone group. After IPW analysis, patients with combined LRT had superior PPS and secondary PFS. The incidence rates of AEs were higher in LRT combination compared to systemic alone (any grade AEs: 94.4 vs. 63.2%, P=0.0422; severe AEs: 33.3 vs. 5.3%, P=0.0422). No significant albumin-bilirubin index changed in the first 3 months in combined LRT group (0.966 [0.647-1.443], P=0.867) though a trend of deterioration in systemic alone group. In conclusion, sequential systemic therapy provides survival benefits after A+B failure. Furthermore, combining LRT with systemic treatment could provide better tumor responses and survival benefits with acceptable toxicity than systemic therapy alone.

Keywords: Rescue therapy, hepatocellular carcinoma, locoregional therapy, tumor response, toxicity

Introduction

Despite significant advancements in the surveillance and management of chronic liver disease, hepatocellular carcinoma (HCC) continues to be one of the leading causes of cancer-related mortality worldwide [1]. While liver resection, radiofrequency ablation, and liver transplantation can potentially cure patients with early-stage HCC, many patients are diagnosed with advanced-stage HCC, which carries a poor prognosis and requires systemic treatment. Sorafenib, a multikinase inhibitor (MKI), has been the first-line therapy for HCC for over a decade. However, the development of atezolizumab and bevacizumab (A+B) as the first-line therapy has changed the treatment landscape, showing significant superiority in terms of overall survival (OS), progression-free survival (PFS), and quality of life [2, 3]. Furthermore, several studies [4-8] have provided some effective rescue therapies for patients who have experienced sorafenib treatment failure. As for patients with A+B treatment failure,

several second-line therapies had possibly provided a better post-progression survival (PPS) [9], but the optimal sequential therapy is still unknown. Recent studies have focused on investigating the efficacy of different systemic treatments after A+B failure [9-11], but the combination with locoregional therapy (LRT) is not well understood. Theoretically, HCC tumor cells can be directly destroyed by LRT, and apoptotic cancer cells can release cancer antigens, enhancing the tumor-killing ability of immune cells [12, 13]. Currently, the combination of transcatheter arterial chemoembolization (TACE) and sorafenib/lenvatinib showed promising survival benefits in patients with unresectable HCC in TACTICS, TACTICS-L, and LAUNCH trials [14-16]. Recently, a phase III study also exhibited significant survival benefits by adding stereotactic body radiation therapy to sorafenib for advanced HCC [17]. Therefore, combining LRT with systemic therapy is a reasonable approach. However, the efficacy and safety of this approach as a sequential therapy after A+B failure have not been reported yet. In this study, we aimed to investigate this issue.

Materials and methods

Patient recruitment

We retrospectively reviewed 142 unresectable HCC patients with A+B treatment between September 2020 and December 2022 at a tertiary medical center in Taiwan. The HCC was diagnosed by pathology or image criteria of the American Association for the Study of Liver Disease [18]. All patients belonged to Barcelona clinic liver cancer (BCLC) stage C or BCLC stage B who were not amenable to locoregional therapy. Nineteen patients were excluded because they were on A+B treatment at the data cut-off date, January 25, 2023. Among 123 patients with discontinuation of A+B treatment, those who discontinued A+B with the reasons of intolerable adverse events (AEs), unafforded financially, complete tumor response, deterioration of liver function to Child-Pugh class C, deteriorated performance status as Eastern Cooperative Oncology Group (ECOG) of 3, lost to follow-up, alpha-fetoprotein (AFP) elevation only, or received sequential therapy in other hospital were excluded. Finally, we analyzed 61 patients had stopped A+B treatment under the evidence of radiological progression. The choice of treatment after A+B failure was suggested in multidisciplinary meetings consisted of hepatologist, surgeon, medical oncologist, radiational oncologist, radiologist, and pathologist. The post-treatment of A+B is determined based on patients' performance status, preserved liver function, prior therapy, and their financial situation. Locoregional therapies were recommended for patients with a significant tumor burden in the liver. Radiotherapy and hepatic arterial infusion chemotherapy (HAIC) were considered for patients with vascular invasion. Finally, the treatment regimens were decided by patients and responsible clinical doctors by shared decision making. The study was approved by institutional review board of Chang Gung Medical Foundation (IRB No. 202300597B0) and written informed consent was waived due to the retrospective design.

Follow-up and outcome evaluation

Serum biochemistry including liver function, renal function and AFP were checked before and every 2-4 weeks post initial sequential therapy. After initiation of sequential therapy, image evaluation with dynamic CT or magnetic resonance imaging (MRI) was performed every 2-3 months. Radiological responses were classified into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to Modified Response Evaluation Criteria in Solid Tumors (mRECIST). ORR and disease control rate (DCR) were assessed as CR plus PR and ORR plus SD, respectively.

PPS defined as the period from the date of radiological progression of A+B treatment to the date of the date of death. Secondary PFS was calculated from the date of initiation of sequential systemic therapy to the date of disease progression or death. For patients alive without radiological PD, we censored at the date of the last follow-up. PPS and secondary PFS were estimated using Kaplan-Meier method and compared subgroup using log-rank test. All of AEs were evaluated by Common Terminology Criteria for Adverse Events v5.0 (NCI CTCAE; version 5.0).

Statistical analysis

Descriptive data are presented as mean ± standard deviation and median (interquartile

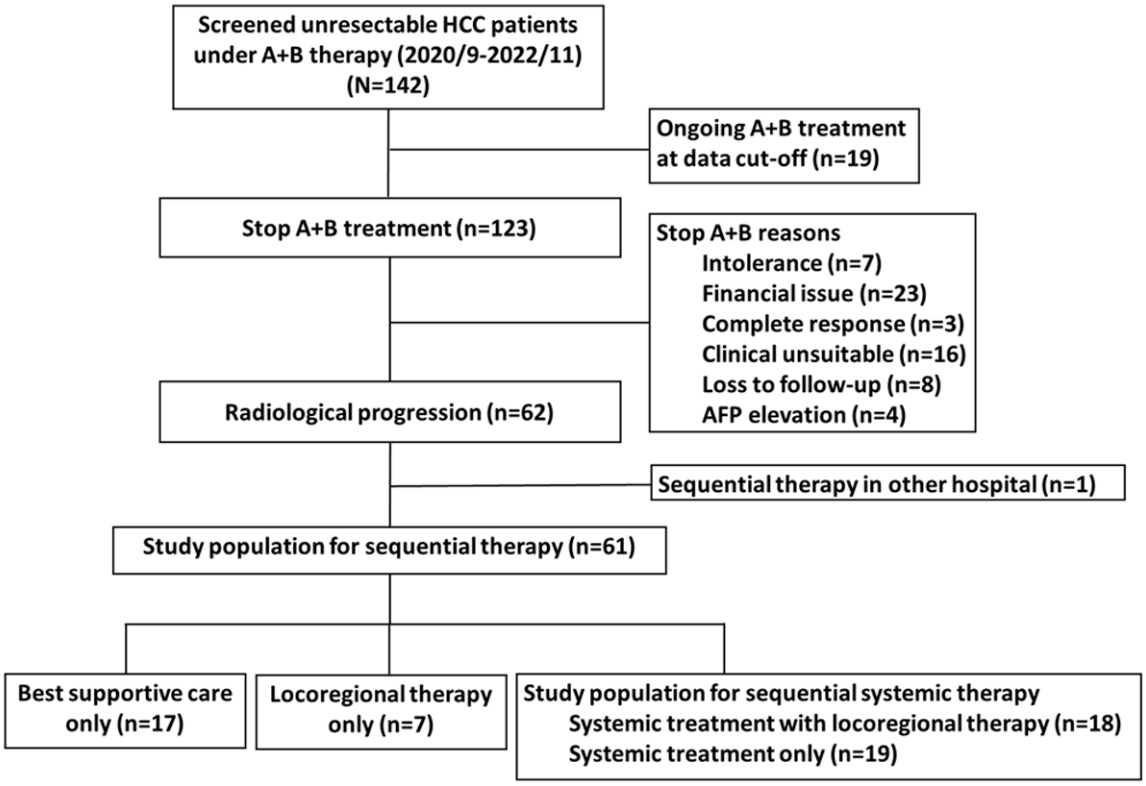

Figure 1. Patient recruitment of the study. HCC, hepatocellular carcinoma; A+B, atezolizumab plus bevacizumab; AFP, alpha-fetoprotein.

range, IQR) for with or without normal distribution, respectively. Independent Student's t-test and Mann-Whitney U test were used to assess differences between groups according to normal and abnormal distribution variables. For categorical variables, we used the Chi-square or Fisher exact test to compare the deference between two groups. Generalized estimating equation method was applied to analyze the change of Albumin-bilirubin index (ALBI) score. Two-tailed *P* value of <0.05 was defined as statistically significant. In order to minimize the differences of characteristics and to reduce confounding factors between patients received sequential systemic treatment with and without LRT, inverse probability weighting (IPW) analysis were applied. IPW was defined as 1 for the sequential systemic treatment with LRT group and (propensity score)/(1 - propensity score) for the sequential systemic alone group adjusting by age, ALBI grade on failure of A+B, and BCLC classification on failure of A+B. We used the statistical software program with SAS version 9.4, SPSS software (release Version 22.0, IBM Corp., Armonk, NY, USA), and STATA (STATA version 14.0; StataCorp, College Station, TX) for statistical analyses.

Results

Clinical characteristics of enrolled patients

A total of 61 patients had discontinued A+B treatment due to radiological evidence of disease progression (**Figure 1**). Baseline characteristics of patients with sequential therapy or best supportive care only were presented in Supplementary Table 1. Before A+B treatment, the median age was 60.7 years old with 83.6% of male gender, 88.5% with underlying chronic viral hepatitis, 85.2% with BCLC stage C, 60.7% no prior systemic treatment before A+B. The liver function reserve belonged to Child-Pugh classes A and B were 80.3% and 19.7%, respectively. On the time of A+B treatment failure, 93.4% of them were BCLC stage C. The liver function reserve categorized as Child-Pugh classes A, B, and C were 57.6%, 33.9%, and 8.5%, respectively. Patients receiving the best supportive care after discontinuation of A+B had relatively poor Child-Pugh class and ALBI

Table 1. Baseline characteristics for patients received sequential systemic treatment with and without LRT

Variables	Received systemic treatment N=37	Combined LRT N=18	Systemic only N=19	*P* value
On treatment of A+B				
Age (years: median (range))	60.8 (33.3-75.6)	60.8 (33.3-75.6)	61.2 (33.9-71.8)	0.8669
<60	17 (46.0)	9 (50.0)	8 (42.1)	0.6301
≥60	20 (54.0)	9 (50.0)	11 (57.9)	
Gender				
Male	32 (86.5)	16 (88.9)	16 (84.2)	1.0000
Female	5 (13.5)	2 (11.1)	3 (15.8)	
Etiology				
Virus	34 (91.9)	16 (88.9)	18 (94.7)	0.6039
Non-Virus	3 (8.1)	2 (11.1)	1 (5.3)	
Prior locoregional therapy				
No	15 (40.5)	7 (38.9)	8 (42.1)	0.8421
Yes	22 (59.5)	11 (61.1)	11 (57.9)	
TACE	19	8	11	
RFA or PEI	6	2	4	
RT	7	2	5	
Resection	1	1	0	
Prior systemic treatment				
1st line	22 (59.5)	13 (72.2)	9 (47.4)	0.1238
≥2nd line	15 (40.5)	5 (27.8)	10 (52.6)	
Sorafenib	9	3	6	
Lenvatinib	5	1	4	
Regorafenib	1	0	1	
Ramucirumab	1	0	1	
Nivolumab	1	0	1	
Pembrolizumab	1	0	1	
During A+B treatment				
Locoregional therapy during A+B				
No	24 (64.9)	11 (61.1)	13 (68.4)	0.6415
Yes	13 (35.1)	7 (38.9)	6 (31.6)	
TACE	2	0	2	
RFA or PEI	2	2	0	
RT	10	5	5	
PFS from A+B (months (IQR))	2.9 (2.0-4.8)	3.0 (2.1-4.7)	2.9 (2.0-5.1)	0.8434
On failure of A+B				
ECOG				
0	12 (32.4)	6 (33.3)	6 (31.6)	0.9093
1 or 2	25 (67.6)	12 (66.7)	13 (68.4)	
BCLC stage				
B	2 (5.4)	2 (11.1)	0 (0.0)	0.2297
C	35 (94.6)	16 (88.9)	19 (100.0)	
Macrovascular invasion				
No	10 (27.0)	5 (26.3)	5 (27.8)	0.9203
Yes	27 (73.0)	14 (73.7)	13 (72.2)	
Extrahepatic spreading				
No	10 (27.9)	4 (21.1)	6 (33.3)	0.4005
Yes	27 (73.0)	15 (78.9)	12 (66.7)	

Child-Pugh class				
A	24 (64.9)	14 (77.8)	10 (52.6)	0.2254
B	12 (32.4)	4 (22.2)	8 (42.1)	
C	1 (2.7)	0 (0.0)	1 (5.3)	
ALBI grade				
I	11 (29.7)	8 (44.4)	3 (15.8)	0.0560
II	23 (62.2)	10 (55.6)	13 (68.4)	
III	3 (8.1)	0 (0.0)	3 (15.8)	

Abbreviations: LRT, locoregional therapy; A+B, atezolizumab plus bevacizumab; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous alcohol injection; RT, radiotherapy; PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin-bilirubin index.

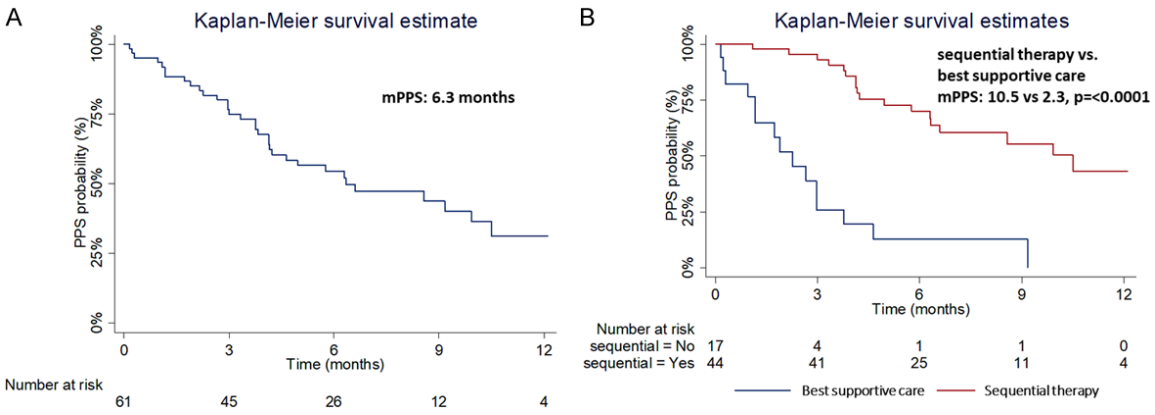

Figure 2. Kaplan-Meier survival function for patients had failure of A+B. A. PPS for overall patients. B. PPS for patients with and without sequential therapy. A+B, atezolizumab plus bevacizumab; PPS, post progression survival.

grade liver function reserve compared to those received sequential therapy (Child-Pugh, P=0.0784, ALBI, P=0.0039).

As shown in **Table 1**, for the 37 patients who received sequential systemic treatment, the median age of these patients was 60.8 years old with 86.5% male gender, 91.9% with underlying chronic viral hepatitis, 59.5% no prior systemic treatment before. On the time of A+B treatment failure, 94.6% of them were BCLC stage C and the prevalence of macrovascular invasion (MVI) and extrahepatic spreading (EHS) were both 73%. Furthermore, there were 18 patients with combination of LRT (48.6%). This included 14 patients treated with TACE, 3 with radiotherapy, one with both TACE and radiotherapy, and one with TACE combined with HAIC. Better ALBI grade liver function reserve was observed in those receiving sequential systemic treatment combined with LRT (P=0.0560). For reducing the selection biases and confounding variables, we then conducted IPW analysis in the later part of this study.

Therapeutic outcome for overall patients

Among 61 patients experienced radiological progression of A+B and the median PPS was 6.3 months (**Figure 2A**). Patients with sequential therapy had significantly longer PPS and then patients received only the best supportive care (10.5 vs. 2.3 months, P<0.0001) (**Figure 2B**). The overall sequential therapy after failure of A+B including 18 patients with systemic treatment plus LRT, 19 patients with systemic treatment only, and 7 patients with LRT only were summarized in Supplementary Table 2. According to the sequential strategy at disease progression, we evaluated the relationship of PPS into four groups as follows: MKIs, ICIs, MKIs plus ICIs, and others which including systemic chemotherapy and LRT alone. As shown in Supplementary Figure 1, there was no significant differences among different sequential systemic treatments in terms of PPS (median PPS for MKIs, ICIs, MKIs plus ICIs, others: not reached, 9.9, 15.4, 6.3 months, P=0.6258).

Table 2. Treatment outcome for patients had sequential systemic therapy with and without LRT

	Received systemic therapy (N=37)	Combined LRT (N=18)	Systemic alone (N=19)	*P* value
Best response by mRECIST				
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	
Partial response	5 (13.5)	5 (27.8)	0 (0.0)	
Stable disease	13 (35.1)	8 (44.4)	5 (26.3)	
Progressive disease	15 (40.5)	5 (27.8)	10 (52.6)	
No image evaluation	4 (10.1)	0 (0.0)	4 (21.1)	
Objective response rate	5 (13.5)	5 (27.8)	0 (0.0)	0.0197
Disease control rate	18 (48.6)	13 (72.2)	5 (26.3)	0.0052
Post A+B observation period (months)	6.6 (IQR: 4.2-10.2)	9.4 (IQR: 7.4-10.6)	5.3 (IQR: 3.8-6.3)	0.0015
Tumor progression before data cut-off date	27 (73.0)	14 (77.8)	13 (68.4)	0.7140
Mortality	18 (48.7)	7 (38.9)	11 (57.9)	0.2476
All grade AE	29 (94.4)	17 (94.4)	12 (63.2)	0.0422
Severe AE (≥ grade 3)	7 (18.9)	6 (33.3)	1 (5.3)	0.0422

Abbreviations: LRT, locoregional therapy; mRECIST, modified Response Evaluation Criteria in Solid Tumors; A+B, atezolizumab plus bevacizumab; AE, adverse event.

Table 3. Combination strategies for sequential systemic treatment with or without LRT (N=37)

Sequential treatment	Systemic alone	Combine TACE	Combine RT
ICI only			
Pembrolizumab	1	1	
Nivolumab plus ipilimumab	2		2
MKI only			
Sorafenib	2	3	
Lenvatinib*	3	2	2
Cabozantinib	2	1	
Regorafenib**	3	1	
Lenvatinib plus ramucirumab		1	
MKI plus ICI			
Lenvatinib plus pembrolizumab	1	5	
Lenvatinib plus nivolumab	2		
Regorafenib plus nivolumab	1		
Cabozantinib plus pembrolizumab	1		
Other			
Mitoxantrone	1	1	

*One patient had sequential lenvatinib combined with TACE and RT. **One patient had sequential regorafenib combined with TACE and HAIC. Abbreviations: LRT, locoregional therapy; ICI, immune check point inhibitor; MKI, multikinase inhibitor; TACE, transcatheter arterial chemoembolization; RT, radiotherapy; HAIC, hepatic arterial infusion chemotherapy.

Therapeutic outcome for sequential systemic and locoregional therapy combination

As for 37 patients received sequential systemic treatment with/without LRT, the median follow-up period was 6.6 months with tumor progression occurred in 27 patients (73.0%) and mortalities observed in 18 patients (48.6%). The details of therapeutic outcome and combination strategies were showed in **Tables 2** and **3**. The ORR and DCR were both significantly higher in patients with sequential systemic treatment with LRT compared with patients without LRT (ORR: 27.8 vs. 0%, P=0.0197; DCR: 72.2 vs. 26.3%, P=0.0052). The median PPS and secondary PFS were significantly longer in patients had sequential systemic treatment with LRT whether before IPW (with LRT vs. without LRT, PPS: 12.2 vs. 5.8 months, P=0.0070; PFS: 5.0 vs. 2.6 months, P=0.0134; **Figure 3A** and **3B**), or after IPW (with LRT vs. without LRT, PPS: 12.2 vs. 6.3 months, P=0.0156; PFS: 5.0 vs. 2.6 months, P=0.0094; **Figure 3C** and **3D**). The subgroup analyses were also exhibited that patients treated with sequential systemic treatment with LRT were superior to sequential systemic treatment alone in terms of PPS in several subgroups (Supplementary Figure 2), including BCLC stage C, ALBI 1 or 2, intrahepatic tumor progression, and no combination LRT during A+B treatment period. The benefits

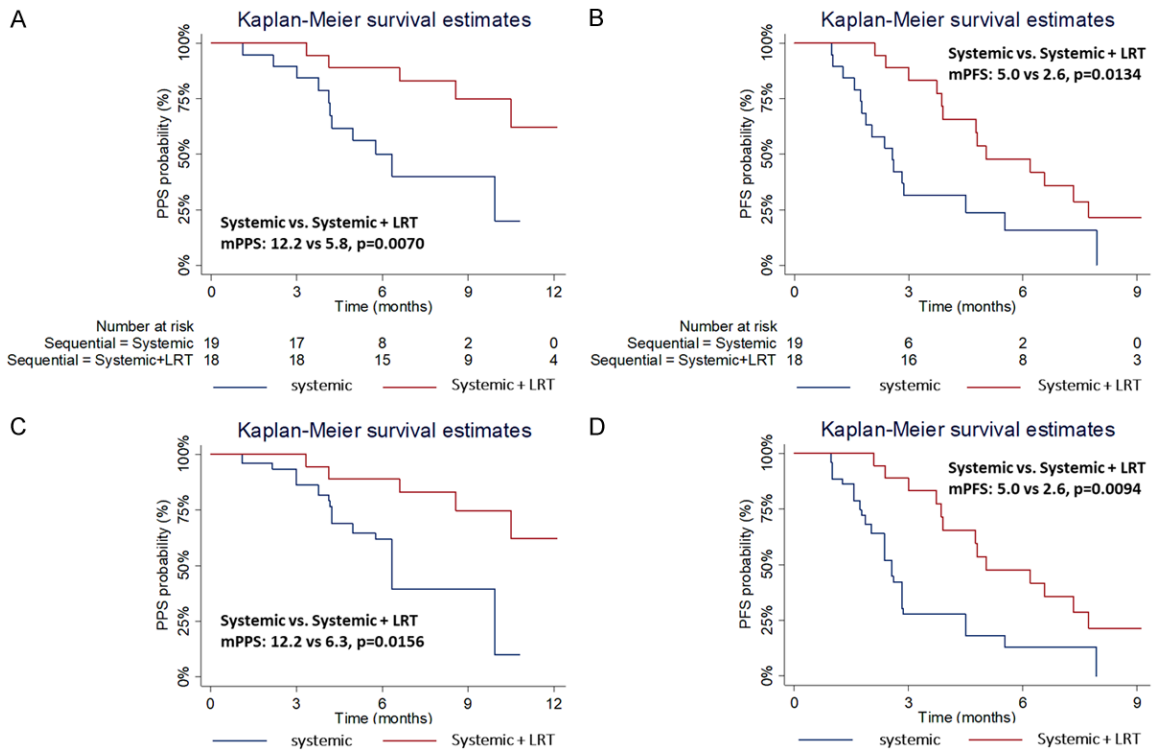

Figure 3. Kaplan-Meier survival function for patients had sequential systemic treatment with and without LRT after failure of A+B. A. PPS before IPW. B. Secondary PFS before IPW. C. PPS after IPW. D. Secondary PFS after IPW. LRT, locoregional therapy; A+B, atezolizumab plus bevacizumab; PPS, post progression survival; PFS, progression-free survival; IPW, inverse probability weighting.

of post progression survival for those patients had extrahepatic tumor spreading, A+B treatment failure pattern as extrahepatic tumor progression, and already combination LRT during A+B treatment were not significant.

Treatment safety for sequential systemic and locoregional therapy combination

The incidence rates of any grade and severe (≥ grade 3) AEs were significantly higher in patient with sequential systemic treatment with LRT compared to those with systemic alone (with LRT vs. without LRT, any grade AEs: 94.4 vs. 63.2%, P=0.0422; severe AEs: 33.3 vs. 5.3%, P=0.0422; **Table 4**). In LRT combination group, the most frequent AEs were hand foot skin reaction, followed by proteinuria, Aspartate aminotransferase (AST) elevation, Alanine aminotransferase (ALT) elevation, hypertension, and dermatitis. On the other hand, hand foot skin reaction, proteinuria, fatigue, AST elevation, ALT elevation, and colitis were mostly observed in systemic treatment alone group. Regarding to severe AEs, one mortality with tumor lysis syndrome was treated with nivolumab and ipilimumab but without LRT combination. Among 6 patients with severe AEs in LRT combination group, one patient with systemic mitoxantrone chemotherapy plus TACE had grade 4 leukopenia and others were grade 3 AEs including hand foot skin reaction, proteinuria, AST and ALT elevation, intra-abdominal abscess, and liver abscess. The changes of ALBI score liver reserve before sequential therapy and 3 months after initiation of treatment were presented in Supplementary Figure 3. There was no statistically significant change in all the patients with sequential therapy (HR, 1.665 [0.836-3.315], P=0.147). Moreover, the ALBI score had a trend of deterioration in systemic treatment alone group but not in LRT combination group (with LRT, HR, 0.966 [0.647-1.443], P=0.867; without LRT, HR, 1.304 [0.996-1,707], P=0.054).

Discussion

Our study aimed to investigate the efficacy and safety of sequential systemic treatment with or

Table 4. Adverse events for patients had sequential systemic therapy with and without LRT

Adverse events	Combined LRT		Systemic alone	
	Any grade	≥ Grade 3	Any grade	≥ Grade 3
Any adverse events	17 (94)	6 (33)	12 (63)	1 (5)
Hand foot skin reaction	4 (22)	1 (6)	3 (16)	0 (0)
Proteinuria	3 (17)	1 (6)	3 (16)	0 (0)
Aspartate aminotransferase increased	3 (17)	1 (6)	2 (11)	0 (0)
Alanine aminotransferase increased	2 (11)	1 (6)	2 (11)	0 (0)
Hypertension	2 (11)	0 (0)	1 (5)	0 (0)
Dermatitis	2 (11)	0 (0)	0 (0)	0 (0)
Intra-abdominal abscess	1 (6)	1 (6)	0 (0)	0 (0)
Liver abscess	1 (6)	1 (6)	0 (0)	0 (0)
Leukopenia	1 (6)	1 (6)	0 (0)	0 (0)
Fatigue	1 (6)	0 (0)	3 (16)	0 (0)
Anorexia or nausea	1 (6)	0 (0)	0 (0)	0 (0)
Pneumonitis	1 (6)	0 (0)	0 (0)	0 (0)
Anemia	1 (6)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	1 (6)	0 (0)	0 (0)	0 (0)
Colitis	0 (0)	0 (0)	2 (11)	0 (0)
Tumor lysis syndrome	0 (0)	0 (0)	1 (5)	1 (5)
Musculoskeletal pain	0 (0)	0 (0)	1 (5)	0 (0)
Blood bilirubin increased	0 (0)	0 (0)	1 (5)	0 (0)
Creatinine increase	0 (0)	0 (0)	1 (5)	0 (0)
Headache	0 (0)	0 (0)	1 (5)	0 (0)
Dysphonia	0 (0)	0 (0)	1 (5)	0 (0)
Mucositis	0 (0)	0 (0)	1 (5)	0 (0)

One patient received systemic mitoxantrone chemotherapy and TACE combination had grade 4 leukopenia. One patient received nivolumab with ipilimumab had grade 5 tumor lysis syndrome. Otherwise, others of severe TRAE were all grade 3 TRAE.

without LRT for HCC patients after A+B failure. Our findings demonstrated sequential therapy after A+B failure provided a superior PPS than best supportive care only which is comparable to prior studies [9]. Importantly, by IPW analysis, the combination of LRT with systemic treatment as sequential therapy achieved significant improvements in both tumor response and survival when compared to those who received sequential systemic treatment alone. Thus, our data indicate that systemic treatment combined with LRT is an effective sequential therapy after A+B treatment failure.

In our study, patients had diverse sequential systemic treatments, including MKI (51.4%), ICIs (16.2%), MKI with ICIs (27.0%), and chemotherapy (5.4%). The most frequent regimens were lenvatinib (16.2%), lenvatinib plus pembrolizumab (16.2%), followed by sorafenib (13.5%), nivolumab plus ipilimumab (10.8%), and regorafenib (10.8%). Theoretically, lenvatinib potently inhibits FGFR4 overexpressed/WNT/β-catenin mutated tumor which recognized as immune exclusion HCC could be an ideal rescue therapy after failure of A+B [10, 19]. Favorable PPS in patients switching to MKI after failure of ICIs had been validated in a large international observational study [20]. Moreover, a recent study demonstrated the superior PFS of lenvatinib but comparable efficacy of OS to sorafenib as second-line treatment after A+B failure [11]. Apart from the central role of MKI, nivolumab plus ipilimumab could be a potential effective and tolerable regimen after failure of ICIs-based combination therapy [21]. However, no superiority of different sequential systemic treatment in terms of PPS in our analysis possibly due to a small-scale study. Therefore, further large-scale study is needed to guide physicians for choosing the different systemic treatments.

TACE is the standard treatment modality for intermediate stage HCC, and a large observational GIDEON study indicated combination of

sorafenib and TACE could be synergistic and effective with longer OS across BCLC stages [22]. Recent phase III studies also demonstrated that adding TACE or radiotherapy to MKI improves efficacy outcomes in treatment naïve unresectable HCC [14-17]. A better survival outcome using sequential regorafenib combined with LRT after failure of sorafenib was also proposed [23]. Here, our study clearly demonstrated that combining LRT with systemic treatment after failure of A+B could offer an additional antitumoral ability, with increase of the ORR to 27.8% and DCR to 72.2% and significantly extended the post progression survival time. By subgroup analysis, patients with BCLC stage C, ALBI grade 1/2 and intrahepatic tumor progression during A+B treatment tended to be benefited from combining with LRT. Interestingly, the advantage of combining with LRT after A+B failure was not obvious for those patients who had combined LRT during the A+B treatment period. These results indicate sequential systemic treatment combined with LRT being an effective treatment choice especially for those progression of intrahepatic tumor and no LRT during the A+B treatment.

Combining systemic treatment with LRT is reasonable but should be carefully evaluated in selected patients in order to avoid increased liver damage [24]. Similar to previous study of sorafenib combined with TACE [22], the systemic treatment combined with LRT in our study significantly increased the rates of any grade AEs and of severe AEs comparing to systemic treatment alone. However, the incidence rate of AE in patients receiving sequential systemic treatment alone could be underestimated because of the extremely short observation period. Nevertheless, the combination of systemic treatment and LRT might pay more attentions on potentially additional AEs [25]. Fortunately, most AEs including severe AEs were manageable in our studies. With regards to liver function reserve, all of patients with sequential systemic treatment combined LRT were able to be evaluated the 3rd-month ALBI score post sequential therapy and showed no deterioration of ALBI score compart to baseline ALBI score on the time of A+B failure. On the other hand, there was a trend of early deteriorated ALBI score for patients with sequential systemic treatment alone that could possibly result from early tumor progression. Overall, the combination of systemic and LRT as sequential therapy for patients with A+B failure could preserve liver function and without unmanageable AEs.

Our study had several limitations, including a retrospective design from a single tertiary center with small sample size. The baseline characteristics for patients with and without LRT had several differences with potential selection bias. For these limitations, we used the IPW analysis to minimize these biased effects, but due to the limited sample size, we could only include age, ALBI, BCLC traditionally known to have a significant impact on prognosis. A large part of our study patients was not treatment-naive before A+B. Besides, the sequential regimens of systemic treatment and LRT are quite diverse and complicated. The comparing efficacies and safeties of different systemic treatment and LRT combination cannot be done because of small patient number. Moreover, the median observation periods were only 6.6 months after failure of A+B, so toxicity may be underestimated. However, even these limitations, our result clearly documented the advantage of combination of systemic therapy with LRT as the sequential therapy after the failure of A+B treatment.

In conclusion, sequential therapy after A+B failure provides survival benefits than best supportive care alone. For patients with reserved liver function, combining systemic treatment with LRT provide better tumor responses and survival benefits with acceptable toxicity than systemic therapy alone. Further studies are required to validate the findings of this preliminary study.

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Disclosure of conflict of interest

None.

Abbreviations

HCC, hepatocellular carcinoma; MKI, multikinase inhibitors; A+B, atezolizumab plus bevacizumab; OS, overall survival; PFS, progression-

free survival; PPS, post-progression survival; LRT, locoregional therapy; TACE, transcatheter arterial chemoembolization; BCLC, Barcelona clinic liver cancer; AEs, adverse events; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; HAIC, hepatic arterial infusion chemotherapy; CT, computed tomography; MRI, magnetic resonance imaging; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; mRECIST, Modified Response Evaluation Criteria in Solid Tumors; CTCAE, Common Terminology Criteria for Adverse Events; ORR, object response rate; DCR, disease control rate; IQR, interquartile range; ALBI, Albumin-bilirubin index; IPW, inverse probability weighting; MVI, macrovascular invasion; EHS, extrahepatic spreading; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.

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Supplementary Table 1. Baseline characteristics for overall radiological disease progression of A+B treated patients

Variables	Overall No. of patients (N=61)	Received sequential treatment No. of patients (N=44)	Best supportive care only No. of patients (N=17)	*P* value
On treatment of A+B				
Age (years: median (range))	60.7 (33.3-83.2)	60.3 (33.3-75.6)	61.2 (36.3-83.2)	0.5138
<60	30 (49.2)	22 (50.0)	8 (47.1)	0.8368
≥60	31 (50.8)	22 (50.0)	9 (52.9)	
Gender				
Male	51 (83.6)	38 (86.4)	13 (76.5)	0.4437
Female	10 (16.4)	6 (13.6)	4 (23.5)	
Etiology				
Virus	54 (88.5)	39 (88.6)	15 (88.2)	1.0000
Non-Virus	7 (11.5)	5 (11.4)	2 (11.8)	
ECOG				
0	32 (52.5)	25 (56.8)	7 (41.2)	0.2727
1 or 2	29 (47.5)	19 (43.2)	10 (56.8)	
BCLC stage				
B	9 (14.8)	8 (18.2)	1 (5.9)	0.4227
C	52 (85.2)	36 (81.8)	16 (94.1)	
Child-Pugh class				
A	49 (80.3)	38 (86.4)	11 (64.7)	0.0564
B	12 (19.7)	6 (13.6)	6 (35.3)	
ALBI grade				
I	21 (35.6)	18 (41.9)	3 (18.8)	0.0802
II	37 (62.7)	25 (58.1)	12 (75.0)	
III	1 (1.7)	0 (0.0)	1 (6.3)	
Missing	2	1	1	
Prior locoregional therapy				
No	29 (47.5)	21 (47.7)	8 (47.1)	0.9629
Yes	32 (52.5)	23 (52.3)	9 (52.9)	
TACE	28	20	8	
RFA or PEI	8	6	2	
RT	9	7	2	
HAIC	1	1	0	
Resection	2	1	1	
Prior systemic treatment				
1st line	37 (60.7)	26 (59.1)	11 (64.7)	0.6873
≥2nd line	24 (39.3)	18 (40.9)	6 (35.3)	
Sorafenib	13	11	2	
Lenvatinib	8	5	3	
Regorafenib	2	2	0	
Ramucirumab	1	1	0	
Cabozantinib	1	0	1	
Nivolumab	2	1	1	
Pembrolizumab	3	1	2	

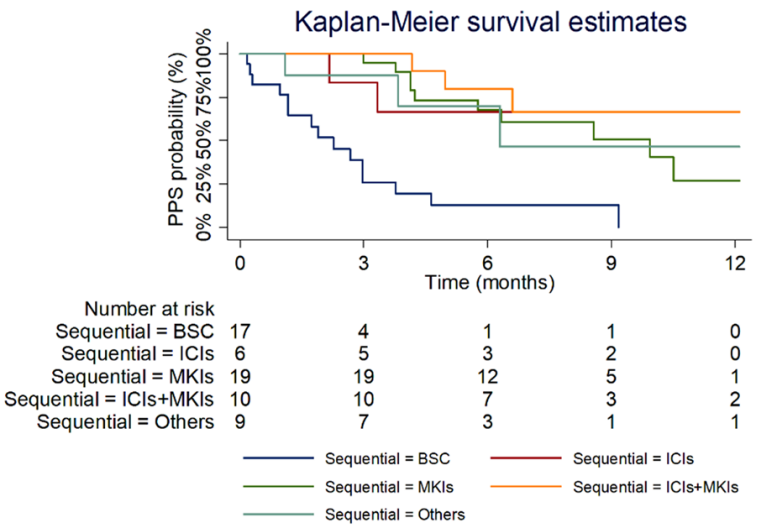
During A+B treatment				
Locoregional therapy during A+B				
No	41 (67.2)	30 (68.2)	11 (64.7)	0.7954
Yes	20 (32.8)	14 (31.8)	6 (35.3)	
TACE	6	4	2	
RFA or PEI	2	2	0	
RT	15	11	4	
PFS from A+B (months (IQR))	2.9 (2.0-4.8)	2.9 (2.1-5.1)	2.5 (1.3-3.3)	0.2154
On failure of A+B				
ECOG				
0	20 (32.8)	15 (34.1)	5 (29.4)	0.7271
1 or 2	41 (67.2)	29 (65.9)	12 (70.6)	
BCLC stage				
B	4 (9.8)	2 (4.5)	2 (11.8)	0.3071
C	57 (93.4)	42 (95.5)	15 (88.2)	
Child-Pugh				
A	34 (57.6)	28 (65.1)	6 (37.5)	0.0784
B	20 (33.9)	13 (30.2)	7 (43.8)	
C	5 (8.5)	2 (4.7)	3 (18.8)	
Missing	2	1	1	
Child-Pugh variation				
Improvement	4 (6.8)	4 (9.3)	0 (0.0)	0.4725
Unchanged	35 (59.3)	26 (60.5)	9 (56.3)	
Deterioration	20 (33.9)	13 (30.2)	7 (43.8)	
Missing	2	1	1	
ALBI grade at PD				
I	13 (22.0)	11 (25.6)	2 (12.5)	0.0039
II	34 (57.6)	28 (65.1)	6 (37.5)	
III	12 (20.4)	4 (9.3)	8 (50.0)	
Missing	2	1	1	
ALBI grade variation				
Improvement	5 (8.6)	5 (11.9)	0 (0.0)	0.4883
Unchanged	31 (53.5)	22 (52.4)	9 (60.0)	
Deterioration	21 (37.3)	15 (35.7)	6 (40.0)	
Missing	4	2	2	

Abbreviations: LRT, locoregional therapy; A+B, atezolizumab plus bevacizumab; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; PEI, percutaneous alcohol injection; RT, radiotherapy; PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin-bilirubin index.

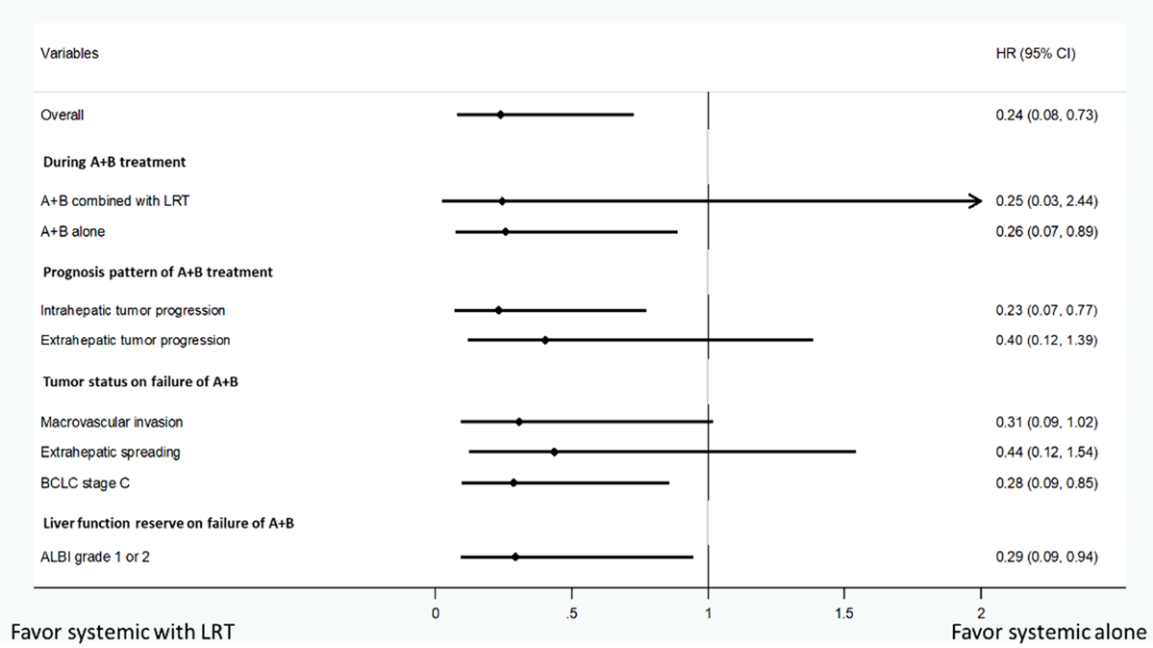
Supplementary Table 2. Sequential treatment for overall radiological disease progression of A+B treated patients

Systemic treatment	37
ICI only	6
Pembrolizumab	2
Nivolumab plus ipilimumab	4
MKI only	19
Sorafenib	5
Lenvatinib	6
Cabozantinib	3
Regorafenib	4
Lenvatinib plus ramucirumab	1
MKI plus ICI	10
Lenvatinib plus pembrolizumab	6
Lenvatinib plus nivolumab	2
Regorafenib plus nivolumab	1
Cabozantinib plus pembrolizumab	1
Other	2
Mitoxantrone	2
Locoregional therapy	25
TACE	20
Radiotherapy	8
HAIC	1

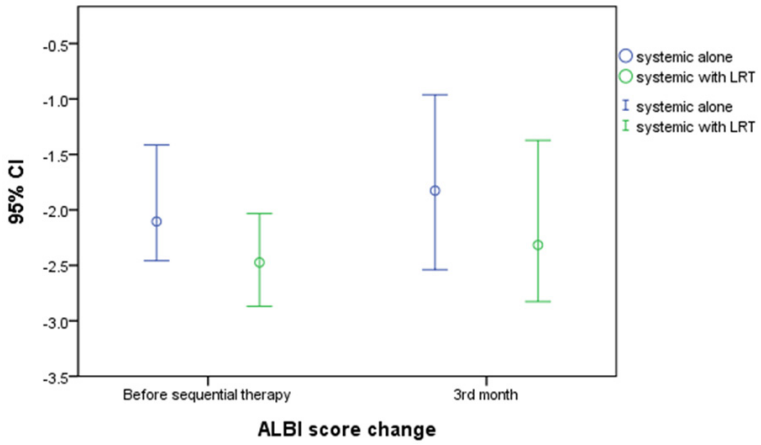
Abbreviations: LRT, locoregional therapy; ICI, immune check point inhibitor; MKI, multikinase inhibitor; TACE, transcatheter arterial chemoembolization; RT, radiotherapy; HAIC, hepatic arterial infusion chemotherapy.



Supplementary Figure 1. Kaplan-Meier survival function of PPS for patients had failure of A+B. PPS, post progression survival; A+B, atezolizumab plus bevacizumab; BSC, best supportive care; ICI, immune checkpoint inhibitor; MKI, multikinase inhibitor; Other, systemic chemotherapy or locoregional therapy only.



Supplementary Figure 2. Forrest plot of post progression survival in subgroups analyses. A+B, atezolizumab plus bevacizumab; LRT, locoregional therapy; BCLC, Barcelona clinic liver cancer; ALBI, albumin-bilirubin index.



Supplementary Figure 3. The patients had A+B failure post-sequential treatment ALBI score in those received systemic alone and systemic with locoregional therapy. A+B, atezolizumab plus bevacizumab; LRT, locoregional therapy; ALBI, albumin-bilirubin index.