Exploratory Analysis to Identify Candidates Benefitting from Combination Therapy of Transarterial Chemoembolization and Sorafenib for First-Line Treatment of Unresectable Hepatocellular Carcinoma: A Multicenter Retrospective Observational Study

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Keywords
Hepatocellular carcinoma · Transarterial chemoembolization · Sorafenib · Predictive factors · Survival benefits

Abstract

Introduction: The benefits of combining transarterial chemoembolization (TACE) and sorafenib (TACE-S) over TACE alone for treatment of unresectable hepatocellular carcinoma (HCC) remain controversial. Yet, such populations are heterogeneous in terms of baseline characteristics. Objective: To investigate the predictors of survival benefits from added sorafenib and identify the potential candidates for TACE-S. Methods: This multicenter observational study was conducted in 17 Chinese tertiary hospitals for patients with unresectable, liver-confined HCC. Eligible patients with performance status score of ≤1 and Child-Pugh score of ≤7 were treated with TACE or TACE-S. Interactions between treatment and baseline variables were evaluated to find indicators for survival benefits, based on which the patients were stratified. Multivariate models adjusted for baseline characteristics or propensity score were used to compare overall survival (OS) and time to tumor progression (TTP). Results: From January 2009 to December 2015, 1,719 consecutive patients received TACE (n = 1,406) or TACE-S (n = 313). Although TACE-S compared with TACE improved TTP (adjusted hazard ratio [HR] 0.75, p = 0.008), no difference in OS was observed (adjusted HR 0.87, p = 0.090). Nevertheless, the tumor burden (sum of maximum diameter of largest tumor [cm] and tumor number) and albumin-bilirubin (ALBI) score independently predicted the survival benefits from added sorafenib (interaction p < 0.001). For patients with either moderate tumor burden (7–13) or low ALBI score (no more than −2.8) defined as candidates, TACE-S prolonged OS (adjusted HR 0.73, p = 0.003) and TTP (adjusted HR 0.72, p = 0.014) compared to TACE alone, whereas its superiority disappeared in non-candidates. Conclusions: Not all unresectable HCC patients but those with moderate tumor burden or low ALBI score achieve survival benefits from TACE-S compared with TACE alone. Future randomized controlled trials focusing on the subset are warranted.

Introduction

Transarterial chemoembolization (TACE) is optimally recommended for patients with compensated liver function and asymptomatic multifocal or large hepatocellular carcinoma (HCC), who are not candidates for resection or transplantation by the American Association for the Study of the Liver Disease/European Association for the Study of the Liver guidelines [1–3]. Unfortunately, the treatment outcomes have a great variation with a median survival of 19.4 months in general patients to around 49.1 months in well-selected patients [4, 5], indicating a high heterogeneity of unresectable HCC [6–8].

After the advent of sorafenib, it has been proposed that combining TACE and sorafenib (TACE-S) might be a “good marriage” for patients with unresectable HCC [9, 10]. Furthermore, its safety and effectiveness have been widely confirmed by several observational studies [11–15]. However, according to a global randomized controlled trial (RCT), TACE-S might not improve the prognosis in a clinically meaningful manner compared with TACE alone for unresectable HCC patients [16], which is consistent with 2 phase III trials conducted in the UK [17], as well as in Japan and South Korea [18]. On the contrary, a recently conducted RCT by Kudo et al. [19] demonstrated the treatment benefits from concomitant sorafenib administration, challenging the recommendations in current guidelines for TACE-S for unresectable HCC [1, 2].

We compared the inclusion criteria of the above RCTs and found an obvious difference in patient selection regarding tumor burden, liver function, and performance status, although
all the trials enrolled patients with unresectable HCC (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000505692). It should be noted that patient characteristics not only determine the natural outcomes directly but also consequently affect the treatment effects and then the actual prognosis [20]. Nevertheless, the correlations between patient baseline characteristics and survival benefits provided (or not) by TACE-S compared to TACE alone have not been investigated in specially designed studies [21]. Thus, 3 questions remain to be answered: (1) whether TACE-S improves survival in the real world; (2) whether baseline characteristics affect the treatment effects of TACE-S; and (3) whether there exists a subset of patients benefiting from TACE-S compared to TACE alone.

In this large multicenter exploratory study, we aimed to evaluate the effects of concomitant sorafenib administration (compared to TACE alone) on prognosis of patients with unresectable HCC; investigate the predictive factors for survival benefits; and then use them to identify the optimal candidates.

**Patients and Methods**

**Patients’ Eligibility**

Study data were extracted from a nationwide database of HCC patients treated at 17 Chinese centers from January 2009 to December 2015. We included the patients who were firstly diagnosed with HCC according to American Association for the Study of the Liver Disease/European Association for the Study of the Liver guidelines and received conventional TACE or TACE-S [1, 2]. Meanwhile, patients meeting one of the following criteria were excluded: (1) presence of macrovascular invasion or extrahepatic spread; (2) Child-Pugh score > 7; (3) Eastern Cooperative Oncology Group performance status > 1; or (4) diffuse tumor. Finally, 1,719 patients were included in the study cohort (Fig. 1). Written informed consent was obtained from all patients before treatment initiation, which consisted of consents to treatment and potential use of clinical data in future investigations. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institute’s committee on human research of participating centers.
Medical Care

According to the study protocol, treatment decisions were made at the discretion of the institutional multidisciplinary liver tumor boards of each enrolled center. All participants were suitable for TACE treatment. Sorafenib was the only concomitant therapy recommended for TACE, especially for patients with large or multiple lesions or tumor-related symptoms (physicians’ propensity). The final treatment decision was consented by individual patients. Before TACE, hepatic arteriography was carried out to evaluate the vascular anatomy and tumor vascularity. During TACE, a vascular catheter was inserted selectively into the tumor-feeding artery with an injection containing a mixture of doxorubicin (10–50 mg) and lipiodol (2–20 mL), followed by embolization using gelatin sponge particles. When residual viable tumors were confirmed or new lesions developed in patients with adequate liver function, repeated TACE was performed. At an initial dose of 400 mg twice daily, sorafenib was initiated before/at/after the day of first TACE and continuously used with no breaks of sequential TACE thereafter. In addition, sorafenib dose modification was based on the presence of toxicity and individuals’ drug tolerance. Typically, patients were encouraged to continue sorafenib therapy, unless unmanageable or life-threatening adverse events occurred. The patients who were concomitantly treated by TACE within 30 days before or after initial TACE were considered to be receiving TACE-S therapy; otherwise, TACE alone. For patients treated with TACE alone, sorafenib was recommended after TACE failure because there was no other effective systemic therapy before the end of the study (December 2015). For patients receiving TACE-S, monotherapy with sorafenib was administered when patients were refractory to TACE because there was no recommended second-line treatment at that time. Additionally, in clinical practice, the sequential treatments were initially recommended by their attending physicians and partially depended on individual patients.

Follow-Up

Laboratory assessment was carried out every 4–6 weeks. Radiological evaluation was recommended during weeks 4 and 8 after treatment and every 8 weeks thereafter using contrast-enhanced computed tomography or magnetic resonance imaging. However, in clinical practice, the intensity of follow-up depended on individuals’ baseline characteristics and responses to the last treatment. The sorafenib-related adverse events and drug tolerance were prospectively recorded in the patients treated by TACE-S. Adverse events were graded using the Common Terminology Criteria for Adverse Events (Version 3.0) from the National Cancer Institute. Overall survival (OS) was defined as the time from TACE initiation until the date of death or last follow-up. Time to tumor progression (TTP) was defined as the time from baseline imaging to tumor progression. Laboratory evaluations were carried out every 4–6 weeks. Radiological evaluation was recommended during weeks 4 and 8 after treatment and every 8 weeks thereafter using contrast-enhanced computed tomography or magnetic resonance imaging. However, in clinical practice, the intensity of follow-up depended on individuals’ baseline characteristics and responses to the last treatment. The sorafenib-related adverse events and drug tolerance were prospectively recorded in the patients treated by TACE-S. Adverse events were graded using the Common Terminology Criteria for Adverse Events (Version 3.0) from the National Cancer Institute. Overall survival (OS) was defined as the time from TACE initiation until the date of death or last follow-up. Time to tumor progression (TTP) was defined as the time from baseline imaging to tumor progression.

Statistical Analysis

Categorical variables were described by frequencies and percentages, and continuous data as mean and SD, or median with interquartile range (IQR). Median OS and TTP were estimated using Kaplan-Meier curves and compared using the log-rank test. The Cox proportional hazards regression model was used to analyze prognostic factors correlated with outcomes, where treatment modality (TACE vs. TACE-S) was used as a stratifying covariate. Considering the impact of baseline characteristics on the treatment assignments and outcomes, we adjusted the difference in outcomes between TACE and TACE-S in 2 multivariate regression models regardless of its performance in univariate analysis (significant or nonsignificant). First, multivariate models included the covariates deemed likely to influence the original treatment assignments (including tumor size [defined by the maximum diameter of the largest tumor], tumor number, and performance status), as well as other variables significantly associated with treatment outcomes according to univariate analyses at a level of 10%. Second, multivariate models included the treatment modality and a propensity score that were calculated from logistic regression using a set of covariates deemed likely to have affected the treatment decisions and all those significant prognostic factors at univariate analyses. Interactions between treatment modality and each baseline variable were tested in univariate Cox regression models and then adjusted in 3 multivariate models by stepwise methods to find the predictors for survival benefits. Patient stratification based on the predictors was conducted accordingly, and the outcome comparisons between TACE and TACE-S were separately performed in different subsets. Considering the decrease in sample size after stratification, boot-strapped analysis was performed by generating 2,000 test datasets comprising 50% analysis dataset by random selection. In addition, the multivariate models had to meet the 10 events per variable principle [22]. Statistical analyses were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).
Results

Patient Characteristics

During 34,678.9 person-months of follow-up, 1,719 eligible HCC patients were included, in whom 1,406 (81.8%) were treated by TACE alone and 313 (18.2%) with TACE-S (Table 1). For TACE-S therapy, there were 3 patterns for concomitant sorafenib initiation: before the day of TACE (229, 73.2%), on the day of TACE (13, 4.2%), and after the day of TACE (71, 22.7%). The median time interval from sorafenib administration to TACE procedure was 2 (IQR 0–3) days before first TACE, and the median duration of sorafenib therapy reached 10.3 (1.9–25.6) months. There were 1,480 (86.1%) patients with hepatitis B virus (HBV) or hepato-

### Table 1. Baseline characteristics for the study patients

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total</th>
<th>TACE</th>
<th>TACE-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>1,719</td>
<td>1,406</td>
<td>313</td>
</tr>
<tr>
<td>Age, mean ± SD*</td>
<td>56.1±12.1</td>
<td>56.7±12.1</td>
<td>53.7±12.0</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,450 (84.4)</td>
<td>1,183 (84.1)</td>
<td>267 (85.3)</td>
</tr>
<tr>
<td>Female</td>
<td>269 (15.6)</td>
<td>223 (15.9)</td>
<td>46 (14.7)</td>
</tr>
<tr>
<td>Etiology, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1,427 (83.0)</td>
<td>1,167 (83.0)</td>
<td>260 (83.1)</td>
</tr>
<tr>
<td>HCV</td>
<td>53 (3.1)</td>
<td>37 (2.6)</td>
<td>16 (5.1)</td>
</tr>
<tr>
<td>Others</td>
<td>239 (13.9)</td>
<td>202 (14.4)</td>
<td>37 (11.8)</td>
</tr>
<tr>
<td>Antiviral treatment, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1,403 (81.7)</td>
<td>1,142 (81.2)</td>
<td>261 (83.4)</td>
</tr>
<tr>
<td>BCLC stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>228 (13.3)</td>
<td>192 (13.7)</td>
<td>36 (11.5)</td>
</tr>
<tr>
<td>B</td>
<td>923 (53.7)</td>
<td>756 (53.8)</td>
<td>167 (53.3)</td>
</tr>
<tr>
<td>C</td>
<td>568 (33.0)</td>
<td>458 (32.6)</td>
<td>110 (35.1)</td>
</tr>
<tr>
<td>Performance status, ECOG score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1,151 (67.0)</td>
<td>948 (67.4)</td>
<td>203 (64.9)</td>
</tr>
<tr>
<td>1</td>
<td>568 (33.0)</td>
<td>458 (32.6)</td>
<td>110 (35.1)</td>
</tr>
<tr>
<td>Child-Pugh score, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1,279 (74.4)</td>
<td>1,029 (73.2)</td>
<td>250 (79.9)</td>
</tr>
<tr>
<td>6</td>
<td>339 (19.7)</td>
<td>290 (20.6)</td>
<td>49 (15.7)</td>
</tr>
<tr>
<td>7</td>
<td>101 (5.9)</td>
<td>87 (6.2)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td>Ascites, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1,646 (95.8)</td>
<td>1,354 (96.3)</td>
<td>292 (93.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>73 (4.2)</td>
<td>52 (3.7)</td>
<td>21 (6.7)</td>
</tr>
<tr>
<td>AFP, ng/mL, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤200</td>
<td>942 (54.8)</td>
<td>778 (55.3)</td>
<td>164 (52.4)</td>
</tr>
<tr>
<td>&gt;200</td>
<td>777 (45.2)</td>
<td>628 (44.7)</td>
<td>149 (47.6)</td>
</tr>
<tr>
<td>Tumor number, median (IQR)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>International normalized ratio, mean ± SD</td>
<td>7.7±4.0</td>
<td>7.7±4.0</td>
<td>7.9±4.0</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L, mean ± SD*</td>
<td>49.4±41.2</td>
<td>50.5±42.3</td>
<td>44.7±35.5</td>
</tr>
<tr>
<td>AST, U/L, mean ± SD*</td>
<td>57.1±41.3</td>
<td>58.1±42.7</td>
<td>52.9±34.3</td>
</tr>
<tr>
<td>Albumin, g/L, mean ± SD*</td>
<td>39.0±5.2</td>
<td>38.8±5.2</td>
<td>40.2±5.1</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L, mean ± SD</td>
<td>17.4±8.3</td>
<td>17.5±8.5</td>
<td>16.9±7.4</td>
</tr>
<tr>
<td>BUN, mmol/L, mean ± SD*</td>
<td>5.3±1.6</td>
<td>5.4±1.6</td>
<td>5.1±1.5</td>
</tr>
<tr>
<td>Scr, umol/L, mean ± SD*</td>
<td>76.4±19.9</td>
<td>75.3±19.8</td>
<td>78.6±19.2</td>
</tr>
</tbody>
</table>

*Variables with significant difference between patients treated with TACE and TACE-S (p < 0.05).

TACE, transarterial chemoembolization; TACE-S, combining TACE and sorafenib; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; AFP, alpha-fetoprotein; Scr, serum creatinine; AST, aspartate aminotransferase; BUN, blood urea nitrogen.
titis C virus (HCV) infection. Among them, 1,065 patients with detectable HBV DNA or HCV RNA received antiviral treatment; 338 patients with undetectable HBV DNA or HCV RNA after previous antiviral therapy continued treatment or follow-up; and 77 patients had missing data. Antiviral treatment was routinely administrated to 1,065 patients with detectable HBV DNA or HCV RNA, and a virological response (as defined by recent guidelines [23, 24]) was achieved in 984 (92.4%) patients during the study period. Additionally, there were 516 patients with available information of TTP (online suppl. Table 2).

**Comparison of Treatment Outcomes**

According to univariate analyses, there were no significant differences between the patients treated with TACE and those receiving TACE-S in terms of OS (22.2 vs. 22.4 months, log-rank $p = 0.952$) and TTP (6.3 vs. 7.3 months, log-rank $p = 0.179$; Fig. 2a). Similarly,
univariate Cox regression analyses demonstrated that the treatment still failed to predict OS (unadjusted hazard ratio [HR] 1.00, \(p = 0.952\)). After adjustment for factors potentially influencing the treatment assignments (performance status, tumor number, and tumor size) and factors correlated with OS (age at treatment, etiology, presence of ascites, \(\alpha\)-fetoprotein [AFP] level, aspartate aminotransferase [AST], albumin, total bilirubin, and urea nitrogen), there remained no difference between TACE and TACE-S (adjusted \(HR = 0.87, p = 0.090\)). Moreover, when the difference was adjusted by propensity score, similar conclusions were reached (adjusted \(HR = 0.92, p = 0.283\)). However, multivariate analyses found that TACE-S performed better than TACE alone for TTP (adjusted \(HR = 0.75, p = 0.013\); Table 2; Fig. 2b). As for the
Table 3. The interaction between baseline variables and treatment modality (TACE vs. TACE-S)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analyses*</th>
<th>Multivariate analyses†</th>
</tr>
</thead>
<tbody>
<tr>
<td>For interaction analyses with treatment modality</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1.01 (0.85–1.19)</td>
<td>1.02 (0.69–1.53)</td>
</tr>
<tr>
<td>Age, per year increase</td>
<td>1.00 (0.99–1.00)</td>
<td>0.99 (0.98–1.00)</td>
</tr>
<tr>
<td>Etiology (HBV vs. non-HBV)</td>
<td>0.96 (0.79–1.16)</td>
<td>1.00 (0.81–1.24)</td>
</tr>
<tr>
<td>Performance status (ECOG score 0 vs. 1)</td>
<td>1.59 (1.27–1.99)</td>
<td>1.80 (1.36–2.40)</td>
</tr>
<tr>
<td>Ascites (positive vs. negative)</td>
<td>1.64 (1.05–2.55)</td>
<td>1.19 (0.73–1.92)</td>
</tr>
<tr>
<td>AFP (&gt;200 ng/mL vs. ≤200 ng/mL)</td>
<td>1.27 (1.03–1.55)</td>
<td>1.43 (1.08–1.89)</td>
</tr>
<tr>
<td>Tumor number, per nodule increase</td>
<td>1.08 (1.03–1.12)</td>
<td>1.11 (1.04–1.17)</td>
</tr>
<tr>
<td>Tumor size, per 1 cm increase</td>
<td>1.02 (1.01–1.04)</td>
<td>1.09 (1.06–1.13)</td>
</tr>
<tr>
<td>International normalized ratio, per 1 increase</td>
<td>0.97 (0.91–1.03)</td>
<td>0.96 (0.87–1.05)</td>
</tr>
<tr>
<td>Alanine aminotransferase, per 1 U/L increase</td>
<td>1.00 (1.00–1.01)</td>
<td>1.00 (1.00–1.01)</td>
</tr>
<tr>
<td>AST, per 1 U/L increase</td>
<td>1.00 (1.00–1.01)</td>
<td>1.01 (1.00–1.01)</td>
</tr>
<tr>
<td>Albumin, per 1 g/L increase</td>
<td>1.00 (0.99–1.00)</td>
<td>0.91 (0.89–0.94)</td>
</tr>
<tr>
<td>Total bilirubin, per 1 μmol/L increase</td>
<td>1.01 (1.00–1.01)</td>
<td>1.03 (1.01–1.05)</td>
</tr>
<tr>
<td>BUN, per 1 mmol/L increase</td>
<td>1.00 (0.97–1.03)</td>
<td>0.95 (0.86–1.05)</td>
</tr>
<tr>
<td>SCr, per 1 μmol/L increase</td>
<td>1.00 (0.99–1.00)</td>
<td>0.99 (0.99–1.00)</td>
</tr>
<tr>
<td>Tumor burden, per 1 increase</td>
<td>1.02 (1.01–1.04)</td>
<td>1.10 (1.07–1.13)</td>
</tr>
<tr>
<td>ALBI score, per 1 increase</td>
<td>1.03 (0.97–1.09)</td>
<td>2.87 (2.10–3.93)</td>
</tr>
</tbody>
</table>

* Interaction effects between treatment modalities and baseline variables were separately tested by univariate Cox regression analyses; † Interaction effects between treatment modalities and baseline variables were adjusted by multivariate Cox regression analyses for propensity score and treatment modality in Model 1, for propensity score, treatment modalities, and those significant interaction terms in Model 1 with a stepwise method in Model 2, for the variables in Model 1 but with the tumor size and number replaced by tumor burden and the albumin and total bilirubin replaced by ALBI score in Model 3.

HR, hazard ratio; HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; TACE, transarterial chemoembolization; TACE-S, the combination therapy of TACE and sorafenib; SCr, serum creatinine; AST, aspartate aminotransferase; BUN, blood urea nitrogen.
sessions of TACE, most of the patients (1,292, 75.2%) received no > 3 sessions of TACE. More importantly, there was no significant difference in times of TACE between patients treated with TACE-S and TACE alone (Mann-Whitney U test, $p = 0.161$; online suppl. Fig. 1).

**Predictors of Survival Benefits for TACE-S**

The interaction effects between treatment modality and baseline variables were separately tested (Table 3). According to univariate analyses, the interaction terms between treatment and performance status, presence of ascites, AFP level, tumor number, tumor size, and AST were significant (interaction $p < 0.05$). After the multivariate adjustment for treatment modality and propensity score, the significant predictors were performance status, AFP level, tumor number, tumor size, AST, albumin, total bilirubin, and serum creatine (interaction $p < 0.05$; Model 1). Thereafter, another multivariate Cox regression analysis, including treatment modality, propensity score, and those significant interaction terms in Model 1, by a stepwise method demonstrated that only 4 variables were independent predictors for survival benefits of added sorafenib, namely, tumor number, tumor size, albumin, and total bilirubin (interaction $p < 0.05$; Model 2). For simplicity and convenience, tumor number and tumor size were replaced by tumor burden, which was defined as the algebraic sum of tumor size (cm) and tumor number. Albumin-bilirubin (ALBI) score was a substitute for baseline albumin and total bilirubin. As expected, the stepwise multivariate analyses found that tumor burden and ALBI score were only significant predictors of survival benefits (both interaction $p < 0.001$; Model 3).

**Impacts of Tumor Burden on Survival Benefits**

As the tumor burden rose, the HR of death increased in both patients treated by TACE and those receiving TACE-S. The lines for them crossed twice, at 7 and 13 (Fig. 3a). According to this, the whole cohort was divided into 3 subsets with low (<7), moderate (7–13), or high (>13) tumor burden. Regardless of which one of the 3 subsets, median OS for patients receiving TACE versus TACE-S was comparable (all log-rank $p > 0.05$; online suppl. Fig. 2a). In multivariate analyses, TACE-S significantly improved OS for patients with moderate tumor burden compared with TACE alone (Model 1: adjusted HR 0.76, $p = 0.027$, bootstrap $p' = 0.041$). Nevertheless, they performed similarly in patients with low (Model 1: adjusted HR 1.09, $p = 0.668$, bootstrap $p' = 0.655$) or high (Model 1: adjusted HR 0.86, $p = 0.261$, bootstrap $p' =
Table 4. Multivariate analyses for OS and TTP in subsets based on tumor burden or/and ALBI score

<table>
<thead>
<tr>
<th>Subsets according to tumor burden</th>
<th>Patients, n (%)</th>
<th>Multivariate analyses for adjusted HR of TACE vs. TACE-S</th>
<th>Baseline variables adjusted for/baseline propensity score generated from</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>model 1*</td>
<td>model 2*</td>
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<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
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<tr>
<td>OS analyses</td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Subsets according to tumor burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low tumor burden</td>
<td>520 (30.3)</td>
<td>1.09 (0.75–1.58)</td>
<td>0.668</td>
</tr>
<tr>
<td>Moderate tumor burden</td>
<td>779 (45.3)</td>
<td>0.76 (0.60–0.97)</td>
<td>0.027</td>
</tr>
<tr>
<td>High tumor burden</td>
<td>420 (24.4)</td>
<td>0.86 (0.65–1.12)</td>
<td>0.261</td>
</tr>
<tr>
<td>Subsets according to ALBI score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low ALBI score</td>
<td>522 (30.4)</td>
<td>0.66 (0.49–0.90)</td>
<td>0.008</td>
</tr>
<tr>
<td>High ALBI score</td>
<td>1,197 (69.6)</td>
<td>0.98 (0.80–1.18)</td>
<td>0.819</td>
</tr>
<tr>
<td>Subsets according to tumor burden and ALBI score</td>
<td>Candidates</td>
<td>1,051 (61.1)</td>
<td>0.73 (0.59–0.90)</td>
</tr>
<tr>
<td></td>
<td>Non-candidates</td>
<td>668 (38.9)</td>
<td>1.09 (0.84–1.41)</td>
</tr>
<tr>
<td>Subsets</td>
<td>Patients, n (%)</td>
<td>Multivariate analyses for adjusted HR of TACE vs. TACE-S</td>
<td>Baseline variables adjusted for/ baseline propensity score generated from</td>
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<tr>
<td></td>
<td></td>
<td>model 1*</td>
<td>model 2*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td><strong>TTP analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsets according to tumor burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low tumor burden</td>
<td>153 (29.7)</td>
<td>0.82 (0.54–1.26)</td>
<td>0.371</td>
</tr>
<tr>
<td>Moderate tumor burden</td>
<td>252 (48.8)</td>
<td>0.71 (0.52–0.96)</td>
<td>0.026</td>
</tr>
<tr>
<td>High tumor burden</td>
<td>111 (21.5)</td>
<td>0.82 (0.51–1.31)</td>
<td>0.400</td>
</tr>
<tr>
<td>Subsets according to ALBI score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low ALBI score</td>
<td>165 (42.0)</td>
<td>0.71 (0.49–1.04)</td>
<td>0.077</td>
</tr>
<tr>
<td>High ALBI score</td>
<td>351 (68.0)</td>
<td>0.79 (0.61–1.03)</td>
<td>0.086</td>
</tr>
<tr>
<td>Subsets according to tumor burden and ALBI score&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidates</td>
<td>330 (64.0)</td>
<td>0.72 (0.56–0.94)</td>
<td>0.014</td>
</tr>
<tr>
<td>Non-candidates</td>
<td>186 (36.0)</td>
<td>0.79 (0.54–1.15)</td>
<td>0.213</td>
</tr>
</tbody>
</table>

* Multivariate Cox regression analyses were used for the adjustment of outcome differences between TACE and TACE-S with baseline variables. ^ Multivariate Cox regression analyses were used for the adjustment of outcome differences between TACE and TACE-S with propensity score. # Bootstrap analyses by generating 2,000 test datasets comprised 50% analysis dataset by way of random selection. * Patients with either moderate tumor burden or low ALBI score were defined as candidates; otherwise, non-candidates.

OS, overall survival; TTP, time to progression; HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SCr, serum creatinine; TACE, transarterial chemoembolization; TACE-S, the combination therapy of TACE and sorafenib.
0.270) tumor burden (Table 4). These findings were confirmed by multivariate analyses adjusted for propensity score: Model 2: adjusted HR 1.03, \( p = 0.862 \), bootstrap \( p' = 0.847 \) in low tumor burden; adjusted HR 0.74, \( p = 0.010 \), bootstrap \( p' = 0.013 \) in moderate tumor burden; adjusted HR 0.86, \( p = 0.270 \), bootstrap \( p' = 0.294 \) in high tumor burden (Table 4 and online suppl. Fig. 2b). According to subset analyses for TTP, only those patients with moderate tumor burden could benefit from TACE-S treatment compared with TACE alone (Table 4 and online suppl. Fig. 2c, d).

**Impact of ALBI Score on Survival Benefits**

As ALBI score increased, the risk of death became more vulnerable in patients receiving TACE-S than those treated by TACE. The 2 lines crossed at a value of -2.8 (Fig. 3b). Based on this cutoff ALBI score, the enrolled patients were divided into 2 subsets with different liver function: low ALBI (no more than -2.8 score) and high ALBI (more than -2.8 score). The median OS for patients receiving TACE versus TACE-S was comparable in the low and high ALBI subsets (both log-rank \( p > 0.05 \); online suppl. Fig. 3A). According to multivariate analyses, TACE-S improved OS in patients with low ALBI score (Model 1: adjusted HR 0.66, \( p = 0.008 \), bootstrap \( p' = 0.011 \)), but not in those with a high score (Model 1: adjusted HR 0.98, \( p = 0.819 \), bootstrap \( p' = 0.842 \); Table 4). The multivariate model adjusted for propensity score confirmed these findings: Model 2: adjusted HR 0.70, \( p = 0.017 \), bootstrap \( p' = 0.027 \) in low ALBI score; adjusted HR 0.98, \( p = 0.871 \), bootstrap \( p' = 0.872 \) in high ALBI score (Table 4 and online suppl. Fig. 3b). Differences in TTP between treatments were not observed in either of the subsets with low or high ALBI score (Table 4 and online suppl. Fig. 3c, d).

**Identifying Candidates for TACE-S Therapy**

Moderate tumor burden and low ALBI score were indicators for survival benefit from TACE-S treatment compared to TACE alone. Therefore, 668 patients with neither indicator were defined as non-candidates for TACE-S, while the other 1,051 patients were candidates (online suppl. Table 3). In total, there were 845 candidates receiving TACE alone and 206 treated with TACE-S; as for non-candidates, 561 and 107 patients were treated with TACE and TACE-S, respectively. The median OS for candidates receiving TACE-S was significantly better than that for patients treated by TACE alone (28.7 vs. 21.5 months, log-rank \( p = 0.033 \)). On the contrary, the median OS for non-candidates receiving TACE-S was inferior to that in patients treated by TACE alone (15.7 vs. 23.1 months, log-rank \( p = 0.005 \); Fig. 4a). Remarkably, the superiority of TACE-S to TACE alone in OS was observed according to both of the 2 multivariate models adjusted for baseline factors (Model 1: adjusted HR 0.73, \( p = 0.003 \), bootstrap \( p' = 0.013 \) and propensity score (Model 2: adjusted HR 0.74, \( p = 0.005 \), bootstrap \( p' = 0.015 \)). Nevertheless, the differences in non-candidates disappeared after the multivariate adjustments with either baseline characteristics (Model 1: adjusted HR 1.09, \( p = 0.510 \), bootstrap \( p' = 0.540 \) or propensity score (Model 2: adjusted HR 1.15, \( p = 0.290 \), bootstrap \( p' = 0.310 \); Table 4; Fig. 4b). Median TTP was comparable between the patients treated by TACE and TACE-S in candidates and non-candidates (both log-rank \( p > 0.05 \); Fig. 4c). However, compared to TACE alone, TACE-S performed better for candidates but similarly for non-candidates according to multivariate analyses adjusted for either baseline variables (Model 1: adjusted HR 0.72, \( p = 0.014 \), bootstrap \( p' = 0.012 \) in candidates; adjusted HR 0.79, \( p = 0.213 \), bootstrap
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Unadjusted curves for candidates
- TACE (n = 845)
- TACE-S (n = 206)
21.5 vs. 28.7 months
Log-rank p = 0.033

Unadjusted curves for non-candidates
- TACE (n = 561)
- TACE-S (n = 107)
23.1 vs. 15.7 months
Log-rank p = 0.005

Adjusted curves for candidates
- TACE (n = 845)
- TACE-S (n = 206)
Adjusted HR 0.74
95% CI 0.60–0.91
p = 0.005

Adjusted curves for non-candidates
- TACE (n = 561)
- TACE-S (n = 107)
Adjusted HR 1.15
95% CI 0.89–1.48
p = 0.290

Unadjusted curves for candidates
- TACE (n = 192)
- TACE-S (n = 138)
6.3 vs. 8.4 months
Log-rank p = 0.952

Unadjusted curves for non-candidates
- TACE (n = 115)
- TACE-S (n = 71)
6.4 vs. 4.7 months
Log-rank p = 0.418

Adjusted curves for candidates
- TACE (n = 192)
- TACE-S (n = 138)
Adjusted HR 0.73
95% CI 0.56–0.94
p = 0.017

Adjusted curves for non-candidates
- TACE (n = 115)
- TACE-S (n = 71)
Adjusted HR 0.85
95% CI 0.59–1.23
p = 0.395

No. at risk
TACE  TACE-S
a  845  206
   522  152
   249  76
   94   15
   34   5
   16   1
   6    0
   4    0
   1    0
   0    0

b  561  107
   363  60
   200  14
   94   6
   39   5
   16   2
   5    0
   2    0
   0    0

TTP, months
Adjusted curves for candidates
- TACE (n = 192)
- TACE-S (n = 138)
Adjusted HR 0.74
95% CI 0.60–0.91
p = 0.005

TTP, months
Adjusted curves for candidates
- TACE (n = 115)
- TACE-S (n = 71)
Adjusted HR 0.85
95% CI 0.59–1.23
p = 0.395

No. at risk
TACE  TACE-S
192  138
   35   31
   16   13
   4    8
   4    3
   1    1
   0    0
   0    0

115  71
   25   14
   10   5
   2    1
   2    0
   0    0
   0    0

a, b, c, d
Discussion

This nationwide multicenter retrospective observational study, by exploring the interactions between patient characteristics and treatment modalities (TACE-S vs. TACE), showed that the treatment effects of added sorafenib varied independently with tumor burden and ALBI score, despite the comparable outcomes for the whole cohort. Subset analyses according to these factors demonstrated that patients with moderate tumor burden or low ALBI score achieved significant survival benefits from concomitant sorafenib administration, indicating the importance of patient selection for combination therapy. Compared with previous trials [16–19], the strength of the current study lies in (1) its multicenter consecutive dataset with large sample size; (2) real-world patients receiving on-demand TACE and/or continuous sorafenib; (3) expanded study population covering all inclusion criteria of previous RCTs; and (4) objective evidence-based patient stratification and well-designed subset analyses according to multivariate interaction and regression analyses, for the first time.

The median OS of 22.2 months for 1,406 patients treated with TACE alone was comparable to that of 19.8 months reported by a recent systematic review on TACE [4]. However, compared to the median OS of nearly 33 months for guideline-recommended TACE candidates in our previous study, the shorter prognosis in the current study might have been caused by the unselected inclusion criteria, particularly enrolling high-risk patients with Eastern Cooperative Oncology Group score >0 and ascites [5]. The added sorafenib demonstrated a median OS of 22.4 months for the remaining 313 patients, with no significant improvement compared to TACE alone, which was consistent with 20.1 and 21.0 months’ OS in the SPACE and TACE-2 trials with similar patient selection criteria [16, 17]. However, it was shorter than 29.7 months in the phase III RCT (Post-TACE) with well-selected patients in Japan and South Korea [18]. The prolonged TTP was demonstrated in the whole cohort analysis for TACE-S compared with TACE alone, but it failed to result in improved OS, indicating the weak relationship between them. Therefore, TTP might provide little information in the context of TACE-S as sorafenib would confer a mere “cosmetic” effect, delaying the appearance of the arterial hyperenhancement, but not blocking the malignant potential.

The Post-TACE trial focused on patients with tumor size <7 cm who responded to TACE but failed to demonstrate improved outcome after the sequential use of sorafenib compared to TACE alone [18]. Radiological response rates after TACE decrease as the tumor burden increases [25]. According to our recent study, the tumor burden was identified as a robust prognostic factor for TACE [5]. In view of these points, the patients with low tumor burden should respond well enough to TACE alone and the sorafenib administration might be of little additional benefit. In the current study, nearly 3 quarters of the patients with low tumor burden (no >7) achieved an objective response on imaging assessment after first TACE (online suppl. Fig. 4). Besides, compared to the median OS of 25 months in untreated BCLC (Barcelona Clinic of Liver Cancer) B1-substage patients (tumor burden within up-to-7 criteria), that of the low-tumor-burden patients in our study was improved to 41.6 months by TACE alone [7]. Nevertheless, no treatment differences were observed between TACE and TACE-S in this subset, indicating that the “ceiling effect” (good enough for TACE alone) might restrict the sorafenib effect. By coincidence, these findings were consistent with the subgroup analyses of a recent RCT (TACTICS) reported by Kudo et al. [19], in which there were no differences between TACE and TACE-S for prolonging progression-free survival in liver-confined HCC.
patients within up-to-7 criteria (low tumor burden) in spite of the positive results for the whole cohort. In addition, TACE might not suit those patients with huge tumors due to its adverse effects on liver function [26]. In particular, the prognosis of patients with large tumors was significantly decreased compared with low or moderate tumor burden [5]. We found no differences in outcomes between TACE-S and TACE alone in high-tumor-burden patients. Therefore, we conclude that TACE might be unsuitable or even harmful for patients with large tumors, and the benefit of concomitant sorafenib might not compensate for the adverse effects of TACE [27]. In addition, the short TTP in patients with high tumor burden (about 3 months) indicates the early failure and refractoriness of TACE. Multitargeted tyrosine kinase inhibitor therapy (only sorafenib available before the end of the study) could be selected for such patients. Therefore, the early shift from TACE alone to sorafenib treatment might narrow the difference from combining TACE and sorafenib. In the TACTICS trial, patients with large tumors (>10 cm) were excluded, which increased the ratio of moderate-tumor-burden patients and resulted in positive findings [19]. In contrast, the negative results in our whole cohort, as well as in the SPACE and TACE-2 trials, could be explained by the dilution effects from their expanded study populations [16, 17]. The response rate to first TACE was higher in both patients with moderate and high tumor burden when combined with sorafenib, but a survival benefit was recorded only in those with moderate tumor burden. Although imaging response is considered to be a surrogate end point of survival, the correlations might vary with baseline characteristics. In our view, the imaging evaluation should be delayed as tumor burden increases [25]. Therefore, we conclude that the correlations between initial response and survival become weaker as the tumor burden increases. In addition, for patients with high tumor burden, liver function might be more vulnerable to TACE or TACE-S due to the larger area of embolization and necrosis. Considering this point, the positive effects of initial response might be balanced by the negative impacts of the weakened liver function in patients with high tumor burden.

According to a global real-world study, sorafenib appeared to be safe and effective across HCC patients with different liver function [28]. However, patients with unresectable HCC are heterogeneous regarding liver function [6, 7, 29]. Along with deterioration of liver function, sorafenib treatment duration is shortened, and the survival benefits from sorafenib might be weakened accordingly [27, 28]. Patients with Child-Pugh B compared with Child-Pugh A cirrhosis had greater frequency of hepatic function deterioration after long-term sorafenib administration [30–32]. Hyperbilirubinemia has been identified as dose-limiting toxicity for sorafenib [33]. Considering these points, patients with poor liver function would benefit less from the use of sorafenib than those with good liver function [27]. According to the ALBI score proposed for assessing the liver function in HCC, the patients with preserved liver function could be further stratified, objectively and accurately [34, 35]. In our study, the patients with low ALBI score had a longer median duration of sorafenib than those with high ALBI score (15.0 vs. 8.2 months, \(p = 0.003\); online suppl. Fig. 5). The former group achieved significant survival benefits from added sorafenib, while the treatment benefits disappeared in the latter group. Therefore, low ALBI score was identified as an indicator of survival benefit from concomitant sorafenib administration.

This study had several limitations. First, the retrospective nature and observational design might have led to bias in treatment assignments that were initially recommended by the tumor boards and ultimately approved by individual patients. In response to this, we adjusted the effects of treatment modalities with variables that potentially impacted either the treatment assignments or outcomes in 2 multivariate models. Importantly, different from RCTs, the observational study design did not have explicit indications of sorafenib discontinuation even after disease progression, which resulted in longer duration of sorafenib treatment than in previous trials. Besides, there were only 516 patients with available information of TTP because of the
study design; the selection bias of which might have been inevitable but controlled by the bootstrap analysis for internal validation to ensure its accuracy. Second, nearly 35.0% of the patients had early-stage single tumor according to the newly updated BCLC staging system [1]. We aimed to find correlations between patient characteristics and survival benefits and used the baseline heterogeneity to interpret the controversial results in previous RCTs. Therefore, our study adopted the selection criteria that ensured full inclusion of all patients enrolled in these trials (online supp. Fig. 6). Third, the moderate tumor burden and low ALBI score could be received as indicators of survival benefits from TACE-S compared to TACE alone, rather than clinical markers for the effectiveness of sorafenib. There might be other predictors that were not included or detected in our study. Only 53 patients (3.1%) had HCV infection, and we did not find a significant interaction between etiology (HCV vs. HBV) and sorafenib administration as previous studies did [36–38]. Some unrevealed factors might be more specific and significant, such as genetic or other biological variables [39, 40]. Finally, the multiple subgroup analyses might have decreased the sample size. Although the internal validation with bootstrap analyses was used and every subset met the 10 events per variable principle, the generalization and extrapolation of our findings should be cautious and future studies are needed [22].

Conclusions

Our study demonstrates that TACE-S improves TTP but not OS compared with TACE alone in managing unresectable HCC. However, the heterogeneity of tumor burden and liver function counteract the differences in treatment outcomes between the 2 modalities. Remarkably, the moderate tumor burden and/or low ALBI score could identify the potential candidates with survival benefits from added sorafenib. Future RCTs should focus on these subsets, as well as validation in patients with different etiologies from both eastern and western cohorts.

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Statement of Ethics

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institute’s committee on human research of participating centers. Written informed consent was obtained from the patients, and the study protocol was approved by the institute’s committee on human research of participating centers.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Z.W., E.W., and G.H.: study concept and design, acquisition of data, analysis and interpretation of data, drafting and revising of the manuscript, statistical analysis, and administrative, technical, or material support. W.B.: acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis, and administrative, technical, or material support. D.X.: acquisition of data, analysis and interpretation of data, drafting of the manuscript, and administrative, technical, or material support. R.D., J.L., Q.W., L.L., J.S., W.M., H.Z., X.P., G.S., X.Z., G.Y., H.S., J.W., Z.L., S.Y., J.L., W.W., X.Z., Y.L., J.L., H.C., W.W., K.L., X.Y., T.Y., J.Y., X.L., J.N., Z.Y., J.X., and D.F.: acquisition of data, critical revision of the manuscript for important intellectual content, and administrative, technical, or material support. All authors approved the final version of the manuscript.

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