Abstract. Aim: To compare clinical outcome in patients with Child-Pugh C hepatocellular carcinoma (HCC) treated with non-transplant therapies and those treated with best supportive care. Patients and Methods: A total of 182 patients with HCC with Child-Pugh C cirrhosis were analyzed. Patients were classified into two groups: patients treated with non-transplant therapies (n=113, treated group) and untreated patients (n=69, untreated group). Furthermore, for reducing the bias in patient selection, a propensity score matching analysis was performed (35 pairs). Results: The median survival time in the treated group was significantly longer than that in the untreated group (1.16 years vs. 0.21 years, p<0.001). After propensity score matching, the median survival time in the treated group remained significantly longer than that in the untreated group (0.95 years vs. 0.17 years, p=0.01). Conclusion: In patients with HCC with Child-Pugh C cirrhosis, those treated with non-transplant therapies might have longer survival than untreated patients.

Hepatocellular carcinoma (HCC) is a major health problem worldwide. It is the fifth most common cancer in men and the seventh in women and the third most common cause of cancer-related death (1-4). In Japan, as well as in other countries, most cases of HCC are associated with viral infections such as hepatitis B (HBV) and hepatitis C (HCV) virus, although in our country, the number of patients with HCC with etiologies other than HBV and HCV has recently been increasing (5, 6). The prognosis for untreated HCC is poor in general, and the curative treatment for this disease comprise of surgical resection, ablative therapies such as radiofrequency ablation and percutaneous ethanol injection, and liver transplantation (1-6). Non-curate therapies for HCC include transcatheter arterial chemoembolization (TACE), transcatheter arterial infusion chemotherapy, radioembolization, molecular targeting therapies such as sorafenib, and radiation therapy (1-10).

Prognosis for HCC in patients with Child-Pugh C cirrhosis is extremely poor. Thus, in these patients, most current HCC practice guidelines recommend liver transplantation for patients within the Milan criteria and best supportive care for patients without Milan criteria (1, 4, 11, 12). However, in Japan, due to the limited number of brain death donors and advanced age of patients with HCC, the Japan Society of Hepatology recommends non-transplant therapies such as transcatheter arterial chemotherapy with or without embolization and ablative therapies even in HCC with Child-Pugh C cirrhosis (13). The number of elderly patients with HCC in our country has been increasing in recent years (14). However, whether patients with HCC with Child-Pugh C cirrhosis treated with non-transplant therapies could obtain survival benefit remains unclear.

The aims of the current study were thus to compare clinical outcome in patients with HCC with Child-Pugh C cirrhosis treated with non-transplant therapies and those treated with best supportive care. Furthermore, for reducing the bias in patient selection, we compared clinical outcome of these two groups using propensity score matching analysis.

Patients and Methods

Patients. Between May 1990 and October 2013, 190 consecutive patients were initially diagnosed as having HCC with Child-Pugh C cirrhosis at the Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan. Out of these, seven patients with ruptured HCC and one patient within Milan criteria who underwent liver transplantation were excluded from the current analysis. A total of 182 patients were thus analyzed in the present study. Patients...
were classified into two groups: patients treated with non-transplant therapies (n=113, the treated group) and untreated patients (n=69, the untreated group). Since there is no clear evidence that non-transplant therapies for HCC improves the survival of patients with Child-Pugh C cirrhosis, all the patients were informed that the potential treatment benefits were unclear and the rates of expected treatment related complications were higher than those in patients with well-preserved liver function. After full explanation of HCC therapy to these patients, whether therapy for HCC was performed was mainly determined by the decision of attending physicians considering tumor burden, performance status and liver functional reserve. In the treated group, transcatheter arterial therapies were performed in 69 patients, percutaneous ablative therapies in 43 patients and surgical resection in 1 patient as an initial therapy for HCC. Transcatheter arterial therapies were performed with the utmost care. In other words, they were performed supraselectively in the most peripheral accessible feeding arteries to avoid irreversible liver failure. In patients with main portal vein tumor thrombus, TACE was not chosen. Overall survival (OS) was compared between the two groups.

All the protocols were approved by the ethics committee of our institution (approval number, 433). Written informed consent was obtained from all patients prior to each treatment, and the study protocol complied with all of the provisions of the Declaration of Helsinki. The present study comprised a retrospective analysis of patient records registered in our database, and all treatments were conducted in an open-label manner.

HCC diagnosis. HCC was diagnosed using abdominal ultrasound and dynamic computed tomographic (CT) scans (hyperattenuation during the arterial phase in all or some part of the tumor and hypoattenuation in the portal-venous phase) and/or magnetic resonance imaging (MRI), based mainly on the recommendations of the American Association for the Study of Liver Diseases (15-18). Arterial- and portal-phase dynamic CT images were obtained at approximately 30 and 120 s, respectively, after the injection of the contrast material. HCC stage was determined using the Liver Cancer Study Group of Japan staging system (19).

Follow-up. Follow-up consisted of periodic blood tests and monitoring of tumor markers, including α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), using chemiluminescent enzyme immunoassays (Lumipulse PIVKAII Eisai; Eisai, Tokyo, Japan). Dynamic CT/MRI scans were obtained every 2-4 months. Retreatment for HCC was considered depending on the patient’s general conditions, tumor stage and background liver function.

Propensity score analysis. For reducing the bias in patient selection, a propensity score matching analysis was performed to examine causal relationships between treatments and clinical outcomes in a retrospective study other than a randomized controlled trial. Clinical variables entered into the propensity model were age, gender, Child-Pugh score, HCC stage, Milan criteria, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Subsequently, a one-to-one match between the treated group and the untreated group was obtained by using the nearest-neighbor matching method (20, 21).

Table I. Baseline characteristics of the treated group and the untreated group. Data are expressed as number or mean±standard deviation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated group (n=113)</th>
<th>Untreated group (n=69)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.4±7.8</td>
<td>64.8±10.0</td>
<td>0.759a</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>72/41</td>
<td>46/23</td>
<td>0.750b</td>
</tr>
<tr>
<td>Cause of liver disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B/C/B and C/unknown</td>
<td>15/70/3/22/3</td>
<td>18/38/1/12/0</td>
<td>0.162b</td>
</tr>
<tr>
<td>HCC stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I or II/III or IV</td>
<td>51/62</td>
<td>18/51</td>
<td>0.012b</td>
</tr>
<tr>
<td>Milan criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within/without</td>
<td>61/52</td>
<td>18/51</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Maximum tumor size (cm)</td>
<td>3.8±2.6</td>
<td>5.5±3.6</td>
<td>0.001a</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/11/12/13/14/15</td>
<td>71/28/8/3/3/0</td>
<td>26/25/7/7/3/1</td>
<td>0.010b</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>85.9±49.8</td>
<td>134.2±133.3</td>
<td>0.001a</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>48.7±28.6</td>
<td>71.4±100.7</td>
<td>0.025a</td>
</tr>
<tr>
<td>Platelets (x10⁵/µm³)</td>
<td>9.3±6.4</td>
<td>12.5±9.3</td>
<td>0.012a</td>
</tr>
<tr>
<td>AFP (ng/ml)</td>
<td>20482±98379</td>
<td>1740±70627</td>
<td>0.821a</td>
</tr>
<tr>
<td>DCP (mAU/ml)</td>
<td>14216±37833</td>
<td>9651±25623</td>
<td>0.428a</td>
</tr>
</tbody>
</table>


Fisher’s exact test. For analysis of OS, follow-up ended at the time of death from any cause, and the remaining patients were censored at the last follow-up visit. The cumulative OS rates were calculated using the Kaplan-Meier method, and tested using the log-rank test. Factors with a p-value <0.05 in univariate analysis were subjected to multivariate analysis using the Cox proportional hazards model. These statistical methods were used to estimate the interval from initial HCC diagnosis. Data were analyzed using SPSS for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as mean±standard deviation (SD). Values of p<0.05 were considered statistically significant.

Results

Baseline characteristics. The baseline characteristics of the patients in the two groups are shown in Table I. The median observation period was 0.96 years in the treated group and 0.17 years in the untreated group. In terms of maximum tumor size (p=0.001), AST value (p=0.001), ALT value (p=0.025) and platelet count (p=0.012), significant differences were observed in the two groups. The proportions of patients with stage I or II HCC (p=0.012), those with HCC within the Milan criteria (p<0.001) and those with lower Child-Pugh score (p=0.010) in the treated group were significantly higher than those in the untreated group, suggesting that treated-group patients had less advanced HCC and better liver functional reserve than the untreated-group of patients.
OS in the two groups. The median survival time (MST) in the treated group [MST=1.16 years, 95% confidence interval (CI)=0.98-1.34 years] was significantly longer than that in the untreated group (MST=0.21 years, 95% CI=0.11-0.31 years) (p<0.001) (Figure 1).

Univariate and multivariate analyses of factors contributing to OS. Univariate analysis identified the following factors as being significantly associated with OS for all cases (n=182): treatment for HCC (p<0.001); Child-Pugh score 10 or 11 (p<0.001); Milan criteria (p<0.001); maximum tumor size >3 cm (p<0.001); AST >80 IU/l (p=0.003); AFP ≥100 ng/ml (p=0.001); and DCP ≥300 mAU/ml (p<0.001) (Table II). The hazard ratios (HRs) and 95% CIs calculated using multivariate analysis for the eight factors that were significant in univariate analysis are detailed in Table II. Treatment for HCC (p=0.003), Child-Pugh score 10 or 11 (p=0.006), AFP >100 ng/ml (p=0.004) and DCP ≥300 mAU/ml (p<0.001) were found to be significant predictors linked to OS in multivariate analysis.

Causes of death in the two groups. During the follow-up period, 86 patients (76.1%) died in the treated group. The causes of death in the treated group were HCC progression in 25 patients, liver failure in 55, and miscellaneous causes in 6. In the untreated group, 56 patients (81.2%) died during the follow-up period. The causes of death in the untreated group were HCC progression in 20 patients, liver failure in 35 and miscellaneous causes in one.

Subgroup analyses. Results of subgroup analyses according to Child-Pugh score, Milan criteria and HCC stage are shown in Table III. In all subgroup analyses, the treated group had significantly longer OS than the untreated group.

Baseline characteristics and OS in the treated and untreated groups after propensity score matching. Baseline characteristics in the two groups (treated group: n=55, untreated group: n=55) after propensity score matching are demonstrated in Table IV. For all analyzed variables, no significant differences were observed, although the AST value in the treated group tended to be lower than that in the untreated group (p=0.055). The MST in the treated group (MST=0.95 years, 95% CI=0.82-1.08 years) was significantly longer than that in the untreated group (MST=0.17 years, 95% CI=0.05-0.39 years) (p=0.010) (Figure 2).

Subgroup analyses after propensity score matching. Results of subgroup analyses after propensity score matching according to Child-Pugh score, Milan criteria and HCC stage are shown in Table V. In patients with Child-Pugh score 10 or 11 (p=0.032) and HCC stage III or IV (p=0.011), the treated group had significantly longer OS than the untreated group.

Comparison of OS of patients treated with transcatheter arterial therapies and untreated patients. The MST in the group treated with transcatheter arterial therapies (n=69, MST=0.86 years, 95% CI=0.52-1.20 years) was significantly longer than that in the untreated group (p=0.001).
We further compared OS between patients treated with transcatheter arterial therapies and those untreated using propensity score matching (n=46 in both groups). The number of patients with Child-Pugh score 10/11/12/13/14, stage I or II HCC and HCC within Milan criteria in each group was similar. The MST in the group treated with transcatheter arterial therapies (MST=0.63 years, 95% CI=0.36-0.90 years) was significantly longer than that in the untreated group (MST=0.22 years, 95% CI=0.0-0.61 years; p=0.044).

Comparison of OS in patients treated with ablative therapies and untreated patients. The MST in the group treated with ablative therapies (n=43, MST= 1.89 years, 95% CI= 1.42-2.36 years) was significantly longer than that in the untreated group (MST=0.22 years, 95% CI= 0.03-0.41 years) (p=0.044).

We further compared OS between patients treated with ablative therapies and those untreated using propensity score matching (n=20 in both groups). The number of patients with Child-Pugh score 10/11/12/13/14, stage I or II HCC and HCC within Milan criteria in each group was similar. The MST in the group treated with ablative therapies (MST=1.77 years, 95% CI=1.47-2.07 years) was significantly longer than that in the untreated group (MST=0.24 years, 95% CI=0.0-0.61 years; p=0.020).

Discussion

As mentioned earlier, for patients with HCC with Child-Pugh C cirrhosis, most current HCC guidelines recommend liver transplantation for patients within the Milan criteria and best supportive care for patients without Milan criteria (1, 4, 11, 12). Thus, few studies examined the treatment outcome in HCC patients with Child-Pugh C cirrhosis treated with nontransplant therapies (13, 22, 23). Hence, we conducted this comparative study and furthermore carried out propensity score matching analysis since selection bias might be present due to the retrospective nature of the current study.

In our analyses, significantly better survival was shown in the treated group than in the untreated group for all cases and in all subgroup analyses, the treated group showed...
significantly better survival than the untreated group. In addition, after propensity score matching, the treated group demonstrated significantly better survival than the untreated group and our multivariate analysis showed that treatment for HCC is an independent predictor linked to OS. These results suggest that non-transplant therapies can be treatment options even in patients with HCC with Child-Pugh C cirrhosis.

It is of interest that patients with stage III or IV HCC in the treated group demonstrated significantly better survival than those in the untreated group, and patients with HCC treated with transcatheter arterial therapies had significantly better prognosis than those in the untreated group even after propensity score matching. In our country, in patients with advanced-stage HCC, transcatheter arterial therapies such as TACE are selected as first-line therapy in general (10). Our results may be attributed to the frequent use and technical improvements of superselective transarterial therapies even in patients with multiple HCC tumors in Japan (10). Nouso, et al. reported that selective use of TACE in patients with HCC with Child-Pugh C cirrhosis provides survival benefit (22). On the other hand, in subgroup analyses in the propensity score matched cohort, no significant difference was observed in patients with Child-Pugh score 12-15 and those with HCC stage I or II in terms of OS. In these populations, liver function-related factors rather than tumor-related factors may be associated with OS.

Pre-treatment DCP level was the strongest predictor associated with OS in the multivariate analysis. Kobayashi, et al. reported that high DCP levels reflect the biological aggressiveness and progression of HCC tumors (24). Even in patients with HCC with Child-Pugh C cirrhosis, tumor aggressiveness may be linked to poorer survival.

There are several limitations to the current study. Firstly, this is a retrospective comparative study. Secondly, in the subgroups, the number of patients was small for statistical analysis. Thirdly, our study cohorts had heterogeneous patient populations with various clinical stages of HCC. Hence, a further larger prospective study is required. However, our study results demonstrated that non-transplant therapies for patients with HCC with Child-Pugh C cirrhosis may improve prognosis.

In conclusion, in HCC with Child-Pugh C cirrhosis, patients treated with non-transplant therapies might have longer survival than untreated patients. Non-transplant therapies for HCC should not be withdrawn based solely on liver function.

Conflicts of Interest

The Authors have not received any financial support for this study and have no conflicts of interest to declare.

Acknowledgements

The Authors would like to thank Haruko Takada for data collection.
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Received February 26, 2014
Revised May 3, 2014
Accepted May 5, 2014