Efficacy of bi-monthly hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma in patients with decompensated cirrhosis

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Background: We have previously reported that the efficacy of bi-monthly hepatic arterial infusion chemotherapy (B-HAIC) was not inferior to that of sorafenib chemotherapy for the treatment of advanced hepatocellular carcinoma (aHCC) in patients with compensated cirrhosis. In this study, we demonstrate the efficacy of B-HAIC in patients with decompensated cirrhosis.

Methods: Forty-five patients with aHCC refractory to transcatheter arterial chemo-embolization (TACE) were treated with B-HAIC and were divided into two groups according to the grade of their hepatic functional reserve: the Child–Pugh A group (n=21) and the Child–Pugh B group (n=24). The overall survival periods, curative responses, and adverse events in each group were retrospectively analyzed.

Results: The efficacy rate and the disease control rate in the Child–Pugh B group (21% and 71%, respectively) were not significantly impaired compared with the rates in the Child–Pugh A group (38% and 67%, respectively). The median survival time and the survival rate at 12 months of patients in the Child–Pugh B group were 422 days and 58.3%, respectively, whereas those in the Child–Pugh A group were 567 days and 70.8%, respectively. Importantly, the hepatic functional reserve of patients in each group did not worsen during the treatment period. Furthermore, the occurrence rate of serious adverse events leading to discontinuation of anti-tumor treatment in both groups was quite limited despite the preserved hepatic functional reserve in these patients.

Conclusions: Given the preservation of hepatic functional reserve afforded by B-HAIC chemotherapy, even in patients with decompensated cirrhosis, we suggest that B-HAIC might be acceptable as an alternative strategy for aHCC patients who do not respond to TACE.

Keywords: Hepatocellular carcinoma (HCC); hepatic arterial infusion chemotherapy (HAIC); cisplatin; chemotherapy; decompensated cirrhosis

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Introduction

Three-quarters of patients with hepatic diseases are concentrated in Asian-Pacific countries, and actually, 80% of patients with liver cancer are unevenly distributed within these regions (http://www.iarc.fr/, Accessed 20 May 2018). On the contrary, the number of liver cancer patients in European and North American countries is also high so that liver cancer, especially hepatocellular carcinoma (HCC), is a neoplasm that has recently attracted significant attention. According to the latest data of the International Agency for Research on Cancer, more than 14 million individuals worldwide have some type of neoplasm, and 8.2 million individuals die each year because of the exacerbation of a given neoplasm (http://www.iarc.fr/, Accessed 20 May 2018). HCC has an incidence of 0.78 million per year and is the sixth most common neoplasm worldwide. The total number of deaths due to HCC is 0.74 million per year, which is the second highest of all cancer-related deaths (http://www.iarc.fr/, Accessed 20 May 2018). On the basis of these data, the ratio of HCC-related deaths to the incidence of this cancer is extremely high (as high as approximately 95%), and therefore, it is no surprise that HCC has a very poor prognosis.

Essentially, approximately 70–90% of HCC cases occur in patients with chronic liver diseases such as chronic hepatitis and liver cirrhosis. The conventional etiologies of chronic liver disease are human hepatitis B virus infection, human hepatitis C virus infection, and an excess consumption of alcohol. Currently, metabolic syndrome and excessive obesity are also known to cause not only fatty liver but also steatohepatitis, which may progress to liver cirrhosis.

Liver cancer is generally diagnosed in an advanced clinical stage because this disease tends to be clinically silent during its early stages. Additionally, clinicians should consider the hepatic functional reserve level of each patient when treatments are selected.

The anti-tumor agents sorafenib and lenvatinib have been shown to be useful for advanced hepatocellular carcinoma (aHCC) (1,2) and are the only two established first-line chemotherapeutic agents. However, both drugs affect the patient’s hepatic functional reserve because of their effects on the metabolic pathway, which functions throughout the liver (3-6). Therefore, the decision to use these agents requires prior appropriate assessments of hepatic functional reserve. Most patients with aHCC have limited normal hepatic function and concomitant disease, and their prognosis depends in part on their hepatic functional reserve.

The 2013 clinical practice guidelines for HCC of the Japan Society of Hepatology (JSH) recommend chemotherapy with either hepatic arterial infusion chemotherapy (HAIC) or an oral molecular targeted drug such as sorafenib for selective transcatheter arterial chemooembolization (TACE) in patients with refractory aHCC. However, these molecular targeted drugs are basically permitted only for patients with compensated cirrhosis and are not recommended for patients with decompensated cirrhosis (7-9). HAIC allows for repetitive delivery of high intrahepatic drug concentrations without the need for synchronous embolization of the hepatic vasculature and results in acceptable toxicity levels.

In this study, we hypothesized that a bi-monthly hepatic arterial infusion chemotherapy (B-HAIC) protocol would be useful for the treatment of patients with decompensated cirrhosis who have aHCC. We then compared this approach with the previously reported outcomes of arterial infusion chemotherapy using a reservoir (10-16). The median overall survival time of patients with decompensated cirrhosis in the B-HAIC group was almost 422 days and was distinctly not inferior to that of patients who received conventional arterial infusion chemotherapy with a reservoir. B-HAIC is simple, easy to manage, and widely available and could be used even in patients with relatively poor hepatic functional reserve, such as those classified with Child–Pugh class B disease.

Methods

Patients

To evaluate the efficacy and safety of B-HAIC for patients with aHCC with cirrhosis, the records of 96 chemo-naive patients who were refractory to TACE or who demonstrated distinct extrahepatic metastatic lesions were reviewed. Qualified patients had been admitted to Nara Medical University Hospital between January 2009 and December 2014 and were enrolled in this retrospective study. Fifty of the 96 patients were then excluded because they received prior treatment with sorafenib after treatment failure of TACE. Forty-five of the 46 cases treated with B-HAIC were finally enrolled and then divided into two different groups according to the grade of their hepatic functional reserve. One patient who died of acute disease progression within 4 weeks after the start of treatment was excluded.
Definitions of TACE failure

The preceding TACE sessions were performed with an emulsion containing anticancer agents and lipiodol followed by the application of gelatin sponge particles. TACE refractory cases were diagnosed according to the guidelines of the JSH and the Liver Cancer Study Group of Japan (17,18). For intrahepatic lesions, TACE failure was defined as ≥2 consecutive ineffective responses of treated tumors (viable lesions >50%) or ≥2 consecutive progressive increases in total tumor counts, despite a prior change in the choice of chemotherapeutic agent or re-analysis of the feeding artery. Ineffective responses were evaluated by computed tomography (CT)/magnetic resonance imaging (MRI) 1–3 months after an adequately performed selective TACE procedure. Other TACE failure criteria included the continuous elevation of tumor marker levels immediately after TACE (although a transient minor decrease could have been observed) and the appearance of vascular invasion and extrahepatic spread. The diagnosis of HCC was based on characteristic radiological findings together with increases in the serum alpha-fetoprotein and/or des-gamma carboxyprothrombin levels.

B-HAIC treatments

For B-HAIC using cisplatin, intra-arterial cisplatin at 65 mg/m² was administered over 30 min via a catheter inserted into the right or left hepatic artery every 8 weeks, for up to six courses or until disease progression or unacceptable adverse events occurred. An infusion of 3,000 mL or more of extracellular fluid was administered on the day of B-HAIC, and an infusion of at least 1,000 mL was given on the next day to avoid renal toxicity effects of the drug. In cases of inadequate urine output, diuretics were administered for several days. The patients who exhibited a good response to the six courses of B-HAIC were then sequentially treated with an implanted 5-fluorouracil reservoir. This treatment was continued so long as it was tolerated by the patient without disease progression or the occurrence of serious adverse effects.

Assessment and statistical analyses

Every 1–2 months, dynamic enhanced CT or MRI was used to confirm the anti-tumor effects of the treatment according to the modified Response Evaluation Criteria in Solid Tumors (19). The overall survival was calculated as the period from the treatment start date to the day of a patient’s death or the final day of confirmed survival. The time to progression was defined as the period from the first day of treatment until the day of the confirmation of tumor progression by radiological image examination. The chi-square test and Mann–Whitney U test were used to compare the patient characteristics and anti-tumor effects between the Child–Pugh A group and the Child–Pugh B group. We calculated the overall survival using the Kaplan–Meier method and compared the differences between groups using the log-rank test. A P<0.05 was considered statistically significant. JMP version 11.2 (SAS Institute Inc.) software was used for all statistical analyses.

Ethical issues

Informed consent for each treatment was obtained from all patients before the initiation of treatment. The Ethics Committee of Nara Medical University Hospital approved this study (approval #000522), which was conducted in accordance with the ethical principles in the Japanese Ethics Guideline for Epidemiological Research (http://www.mhlw.go.jp/file/06-Seisaku_jouhou-10600000-Daijinkanboukousei_kagakuka/0000080278.pdf, Accessed 20 May 2018).

Results

Patient characteristics

Of the 385 patients with HCC in our hospital during the data generation period, only the following 96 patients were included in the study: those with aHCC, those who were refractory to TACE, those who had undergone adequate radiological imaging assessments, and those who had undergone sufficient blood tests. We then decided to exclude 50 patients treated with sorafenib and another patient, as explained in the patients and methods section. We were left with the records of 21 patients with compensated cirrhosis (Child–Pugh class A disease) and 24 with decompensated cirrhosis (Child–Pugh class B disease) (Figure 1). The average interval between the B-HAIC cycles in the Child–Pugh class A group and the Child–Pugh class B group was 1.9±0.4 and 1.8±0.6 months (mean ± SD), respectively, and the average number of repeated cycles was 3.3±2.0 and 3.0±1.2 times, respectively. The total duration of the B-HAIC treatment averaged 6.2±3.7 and 6.1±3.4 months, respectively, for the Child–Pugh class A and Child–Pugh class B groups. The profiles of patients with aHCC in both
groups are shown in Table 1. The patients in the Child–Pugh class A group (n=21) and the Child–Pugh class B group (n=24) with aHCC were quite similar in age, sex, and preceding treatment ratio. Patients in both groups exhibited no extrahepatic metastasis (with one exception each) and were not significantly different in terms of the classifications of number or the clinical stage of HCC.

**Efficacy and adverse events**

In this retrospective cohort study, the best clinical response and overall survival rate for each group are shown in Figure 2A,B. The disease control rate (Child–Pugh class A: 67%, Child–Pugh class B: 71%) was similar in both groups, whereas the efficacy rate was almost twice as much in the Child–Pugh class A group (38% vs. 21%, P=0.20). The calculated overall survival period of the Child–Pugh class A group was significantly longer than that of the Child–Pugh class B group. The median survival time and the survival rates at 6, 12, and 24 months were 567 days and 79.2%, 70.8%, and 33.3%, respectively, in the Child–Pugh class A group patients and 422 days and 79.2%, 58.3%, and 8.3%, respectively, in the Child–Pugh class B group patients. Importantly, the hepatic functional reserve in the patients of both groups did not change significantly during the treatment period (Figure 3A). We observed no detrimental effects on renal function in patients of both groups (Figure 3B).

The main reason for treatment discontinuance in the Child–Pugh class A group patients was disease progression (19 out of 21 cases: 90.4%), whereas 20% of patients (5 out of 24 cases) in the Child–Pugh class B group did not continue their treatment because of other reasons such as adverse physical events (Figure 3C). However, no significant difference was observed between these two groups. Patients in the Child–Pugh class A group exhibited a higher rate of additional chemotherapy such as 5-fluorouracil-based regimens and/or sorafenib after the end of the B-HAIC treatments compared with patients in the Child–Pugh class B group (Figure 3D).

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**Table 1** Profiles of HCC patients with liver cirrhosis in this study (n=45)

<table>
<thead>
<tr>
<th>Hepatic functional reserve</th>
<th>Child A (n=21)</th>
<th>Child B (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, median)</td>
<td>44–88 [69]</td>
<td>56–82 [72]</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>16/5</td>
<td>19/5</td>
<td>NS</td>
</tr>
<tr>
<td>HCC numbers (1–3/4 and over)</td>
<td>6/15</td>
<td>5/19</td>
<td>NS</td>
</tr>
<tr>
<td>Metastasis (with/without)</td>
<td>1/20</td>
<td>1/23</td>
<td>NS</td>
</tr>
<tr>
<td>HCC clinical stage (II/III/IV)</td>
<td>3/13/5</td>
<td>11/11/2</td>
<td>NS</td>
</tr>
<tr>
<td>T factor (T2/T3/T4)</td>
<td>3/14/4</td>
<td>9/13/2</td>
<td>NS</td>
</tr>
<tr>
<td>Preceding Tx. (with/without)</td>
<td>21/0</td>
<td>24/0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Categorical variables were tested with Fisher’s exact test and continuous variables with Welch’s two sample t-test. HCC, hepatocellular carcinoma; NS, not significant.
Discussion

According to the current guidelines for the appropriate use of molecular targeted drugs against HCC, these drugs should be prescribed only for patients with compensated cirrhosis and chronic hepatitis (7-9). On the contrary, a B-HAIC regimen can be applied not only in patients with compensated cirrhosis but also those with decompensated cirrhosis that is classified as Child–Pugh class B disease.

In this study, we found that the average disease control rate in the patients with decompensated cirrhosis reached 70% and that their median survival time and survival rate at 12 months were 422 days and 58.3%, respectively (Figure 2A,B). The modest outcome of median survival period in decompensated cirrhotic patients compared to that of compensated patients was not due to their poor reactivity on B-HAIC but to the levels of their own hepatic functional reserve at the beginning of B-HAIC. Importantly, the hepatic functional reserves of these patients did not worsen during the whole treatment period as it did in those with compensated cirrhosis (Figure 3A).

Currently, to cure HCC in a specific patient, various options such as surgical resection, radio frequency ablation, and several types of chemotherapeutic agents are available. TACE, which was first established in Japan in 1978, has been shown to be more effective than the best supportive care by randomized control studies and two meta-analyses (20-28). However, this chemotherapy regimen can cause the loss of a patient’s hepatic functional reserve (29-31). For cirrhotic patients whose life expectancy depends on their hepatic functional reserve (32,33), to maintain their own hepatic functional reserve at as high a level as possible should be indispensable for any effective treatment for HCC.

Moreover, in cases of conventional HAIC, a reservoir device should be semi-permanently placed into the intrahepatic arterial space. In contrast, our B-HAIC does not require any transient device, but rather, a vascular puncture for catheter manipulation is generated for each infusion (34). Actually, conventional HAIC using a transient device is considered superior because the activity of the fine-powder formulation of cisplatin used in the puncture infusion method appears to have only modest anti-tumor activity and can be conducted only every 4–6 weeks (35-37). On the contrary, the complication rates related to the use of a transient device (hepatic artery obstruction, pseudo arterial aneurysm formation, and port-related problems) are high (approximately 50%) (10,11). Additionally, some of these complications could negatively impact a patient’s hepatic functional reserve. For these reasons, personnel who administer long-term repeated hepatic arterial chemotherapy infusions with a reservoir need to be well-versed in the technique.

We hypothesized that B-HAIC might be better even for patients with relatively poor hepatic functional reserve because B-HAIC is simple, easy to manage, and is not frequently associated with complications (34). In this study, we demonstrated that the hepatic functional reserve and renal function were not significantly decreased during the entire treatment period of B-HAIC in patients with HCC.
As a physical aspect, the non-invasiveness of B-HAIC might explain the satisfactory overall survival period; those patients were also at an advantage compared with patients in whom a chemotherapy reservoir was placed.

For patients with compensated cirrhosis and HCC that was refractory to TACE, HAIC would have an efficacy no less than that of sorafenib, although the outcomes after either sorafenib or HAIC treatment in patients with aHCC are still controversial (38-40). However, as already mentioned above, patients with decompensated cirrhosis with aHCC are not regarded as good candidates for molecular targeted therapy (7-9).

In this retrospective cohort study, we showed the efficacy of B-HAIC in patients with decompensated cirrhosis and aHCC. Even though our study included only a small group of patients with aHCC, the disease control rate and overall survival rate of patients classified as Child–Pugh class B who were treated with B-HAIC were not inferior to those of patients treated with conventional HAIC with a reservoir, as has been published (10-16).

The patients with decompensated cirrhosis in this study were effectively treated with B-HAIC without any serious adverse events. From the viewpoint of maintaining hepatic functional reserve, the sequential combination method of chemotherapy, which consists of the initial administration of B-HAIC and the sequential use of conventional HAIC, might lead to favorable outcomes.

Actually, the patient population in our study is not sufficiently large as in other reports (11-14), and because our study is retrospective, we could not adjust for the prevalence of some clinical factors such as age, gender, clinical stage of HCC, and sequential adjuvant chemotherapy. However, we regarded the hepatic functional reserve of cirrhotic patients as the most important factor in the treatment of their hepatic neoplasms. This is why we divided the patients in this study into two different groups according to their Child–Pugh classification and why we performed this clinical study.

In our hospital, we established the maximum number of B-HAIC cycles at six to avoid serious adverse events and if
we needed to change the primary B-HAIC regimen, even in cases where it was absolutely effective, to conventional HAIC, which consists of cisplatin and 5-fluorouracil with a transient device.

Notwithstanding some limitations, our present study is the first to demonstrate the efficacy of B-HAIC in patients with decompensated cirrhosis whose disease is classified as Child–Pugh class B. As shown in Table 2, several reports have demonstrated the usefulness of reservoir chemotherapy for fluorouracil–cisplatin regimens in patients with liver cirrhosis with Child–Pugh class A and B disease and small HCC. The median survival time of the patients in these reports ranges from 5.1 to 10.2 months (10-16), and none of the survival times were better than the survival period of patients who were treated with our B-HAIC method.

Thus, our results show that B-HAIC preserves hepatic function even in patients with decompensated cirrhosis, which suggests that B-HAIC might be acceptable as an alternative strategy for patients with small HCC who do not respond to TACE.

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**Table 2** Reports on the outcomes of 5-fluorouracil/cisplatin therapies on advanced HCC (repeated every 2–4 weeks)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Adverse events</th>
<th>Cases*</th>
<th>MST^a (months)</th>
<th>Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Child A</td>
<td>Child B</td>
</tr>
<tr>
<td>Miyaki (13)</td>
<td>2012</td>
<td>17%</td>
<td>249</td>
<td>173</td>
<td>76</td>
</tr>
<tr>
<td>Oh (11)</td>
<td>2013</td>
<td>43%</td>
<td>54</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Niizeki (12)</td>
<td>2012</td>
<td>14%</td>
<td>71</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>Tsai (14)</td>
<td>2014</td>
<td>2%</td>
<td>58</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Terashima (15)</td>
<td>2014</td>
<td>19%</td>
<td>27</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Song (10)</td>
<td>2014</td>
<td>56%</td>
<td>50</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Shao (16)</td>
<td>2013</td>
<td>26%</td>
<td>23</td>
<td>19</td>
<td>4</td>
</tr>
</tbody>
</table>

*: number =532 (total), 343 (Child A), 189 (Child B). ^a: mean ± SD =7.9±1.5 (total), 8.6±0.9 (Child A), 4.7±0.7 (Child B). HCC, hepatocellular carcinoma; MST, median survival time; CR, complete response; PR, partial response; SD, stable disease; PD, progress disease; N/A, not applicable.

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**Footnote**

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The Ethics Committee of Nara Medical University Hospital approved this study (approval #000522). Informed consent for each treatment was obtained from all patients before the initiation of treatment.

**References**


