Treatment of Hepatocellular Carcinoma with Child-Pugh C Cirrhosis

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Key Words
Hepatocellular carcinoma · Child-Pugh C cirrhosis · Liver transplantation

Abstract

Background: In most guidelines, no other interventional therapy but liver transplantation is recommended for the treatment of hepatocellular carcinoma (HCC) with Child-Pugh C cirrhosis (CP-C). However, in Japan, patients were sometimes treated with expectation of benefit. Summary: A workshop was conducted to explore the state of treatments for CP-C HCC in Japan. After the workshop, a questionnaire on therapies was given to the panelists. Clinical data of 769 patients with CP-C HCC from 8 hospitals as well as analyses of data collected by the Liver Cancer Study Group of Japan (LCSGJ) consisting of 1,344 CP-C HCC cases were presented. Patients who underwent liver transplantation were excluded. In total, 424 out of the 769 patients (55.1%) from the 8 hospitals and 537 out of 828 CP-C HCC cases (64.8%) from the LCSGJ data received interventional therapies, such as local ablation and transcatheter arterial chemoembolization. All panelists agreed that there was a subgroup of CP-C patients who benefitted from the locoregional therapies. The major goals for the therapies were to prevent HCC rupture and avoid obstruction of major vessels by tumor growth, which can lead to a sudden deterioration of the patients’ condition. Patient liver function and tumor stage are both important factors for the decision to undergo treatment; however, the inclusion criteria for the treatments varied among the centers. Key Message: There exists a subgroup of CP-C patients who benefit from interventions for HCC.

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Introduction

At the 50th Annual Meeting of the Liver Cancer Study Group of Japan (LCSGJ), which was held in Kyoto in 2014 (congress president: Prof. Masatoshi Kudo), a workshop on the subject ‘treatment of hepatocellular carcinoma (HCC) with Child-Pugh C cirrhosis (CP-C)’ was conducted. Recommended therapies for these patients include best supportive care from major treatment algorithms determined by the Japan Society of Hepatology [1], the American Association for the Study of Liver Diseases, and the European Association for the Study of the Liver [2, 3]. Liver transplantation [4–8] could be an alternative therapy when patients are younger than 65 years and the HCC is within the Milan criteria in the Japanese guidelines [9]. However, since the majority of HCC patients are older than 65 years and a shortage of donors has been a consistent problem in Japan, many patients instead receive locoregional therapies [10, 11] in clinical settings. At present, no concrete evidence exists for the recommendable treatment of CP-C HCC patients except for liver transplantation. However, we often experience cases in which treatment definitely prolongs survival, and there are several reports demonstrating the efficacy of treatments for CP-C HCC [12–19].

This workshop was conducted to elucidate the present status of treatments of CP-C HCC patients among Japanese high-volume centers and to identify subgroups of patients who might be able to receive a survival benefit with such locoregional treatments. After the congress, a questionnaire survey about CP-C HCC treatments was administered to the panelists.

Summary of the Workshop

Nine doctors from different institutes all over Japan, including the Kurume University, Osaka Red Cross Hospital, Ogaki Municipal Hospital, Kanazawa University, Okayama University, Yame General Hospital, Hiroshima City Hospital, Fujita Health University, and Kinki University, presented their research at this workshop. All panelists analyzed the cases of CP-C HCC at their own hospitals, except for the panelist from the Kinki University who used data collected by the LCSGJ from more than 800 medical institutions, consisting of a total of 58,886 patients with primary liver cancer.

Experiences in Individual Facilities

Clinical data of 769 CP-C HCC patients from 8 hospitals were presented. Although CP-C HCC patients might not be treated at community hospitals, 424 out of the 769 patients (55.1%) received interventional treatment [e.g., radiofrequency ablation, transcatheter arterial chemother embolization (TACE), etc.] at hospitals with which the panelists were associated.

In general, only low-risk patients were selected for the therapies; therefore, most presentations showed that the patients who received interventional treatments lived longer than the patients who did not undergo these treatments. Therefore, a considerable amount of bias existed for the beneficial effects of the treatments; however, several panelists conducted propensity score-matched analyses and multivariate analyses to compensate for potential bias. Data presented by the Osaka Red Cross Hospital (n = 265) indicated that, when conducting locoregional therapies, a low Child-Pugh score and low α-fetoprotein or des-gamma-carboxy prothrombin levels were indicators of a good prognosis. The investigators therefore concluded that the effects of the locoregional therapies were evident, especially in cases with a low Child-Pugh score and advanced HCC. Data from the Ogaki Municipal Hospital showed similar results, suggesting that bilirubin, tumor stage, and treatment type were prognostic factors.

Beneficial effects of branched-chain amino acids, short-term hepatic arterial infusion chemotherapy [20], and laparoscopic surgery [21, 22] for protruded HCC with a low Child-Pugh score were reported from the Hiroshima City Hospital, Yame General Hospital, and Fujita Health University, respectively. The importance of residual liver function for prolonged survival was reported from the Kurume, Kanazawa, and Okayama Universities.

The possible improvement of liver function using nucleotide analogues in patients with hepatitis B virus infection was another topic of discussion.

Analysis of Data from the LCSGJ

Kitai and colleagues conducted a multivariate analysis and a propensity score-matched analysis of CP-C HCC patients enrolled in the database of the LCSGJ. There were 1,344 informative CP-C HCC cases, and the analysis was conducted with 1,236 cases after eliminating patients who underwent liver transplantation. As a result of the multivariate Cox proportional hazard analysis and propensity score-matched analysis, the investigators identified treat-
ment type, small tumor size, young age, and low Child-Pugh score (CP-10&11) as indicators of a good prognosis, revealing the beneficial effects of local ablation therapy and TACE in patients with a low Child-Pugh score.

**Results of the Questionnaire Survey**

The questionnaire consisted of 9 simple questions. A summary of the answers is shown in table 1. All panelists agreed that there was a certain subgroup of patients who benefitted from the treatment (A1). Approximately one half of the panelists considered that a treatment effect could be realized when the tumor stage was no more than III (A5). One reason for excluding stage IV HCC is that chemotherapies [23] are too invasive for patients with poor liver function. However, one panelist did not select patients with stage I HCC as candidates for treatment because early HCC takes time to progress to a life-threatening stage. In other words, this panelist does not treat stage I HCC because the deterioration of liver function, as a natural course of CP-C, is much faster than the cancer progression. While this idea appears logical, it must be proven by evidence.

In terms of liver function as a prognostic factor for treatment, one half of the panelists suggested that the upper Child-Pugh score limit should be 11 (A6). Although small differences in the limit score were observed, there was a consensus that patients with very poor liver function should be excluded from therapies because even a small deterioration of liver function as a consequence of these therapies might be life-threatening.

All panelists selected ‘prolongation of patients’ survival’ as the reason to conduct active therapies, and ‘satisfaction of the patients’ was selected as a concomitant reason for treatment by 3 panelists (A7). All panelists felt that the prevention of HCC rupture by therapies leads to a prolongation of survival (A8). The prevention of vascular invasion that results in the immediate deterioration of liver function and control of tumor growth were the second most common reasons for the survival benefit. Bridging therapies to liver transplantation were another reason [14, 15]. Additional comments advocating that therapies should be selectively targeted and that the preservation of

<table>
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<tr>
<th>Questions</th>
<th>Answers</th>
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<tr>
<td>Q1  Are there patients who benefit from interventional treatment?</td>
<td>A1  9 Yes (100%)</td>
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<tr>
<td>Q2  Interventional treatments should not always be applied to all patients.</td>
<td>A2  9 Agree (100%)</td>
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<td>Q3  Does treatment selection depend on the Milan criteria?</td>
<td>A3  6 Yes (66.7%)</td>
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<td>Q4  What is the reason for your answer? (cause of death? please specify)</td>
<td>A4  Most of the answers revealed that liver function and tumor stage are factors influencing treatment choice</td>
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<td>Q5  Which HCC stages are candidates for treatment? (I, II, III, IVa, IVb)</td>
<td>A5  Up to II (n = 1), up to III (n = 6), all stages (n = 1), II–IV (n = 1)</td>
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<td>Q6  What is the maximum Child-Pugh score for treatment?</td>
<td>A6  Up to 10 (n = 1), up to 11 (n = 5), up to 12 (n = 2), up to 13 (n = 1)</td>
</tr>
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<td>Q7  What is the goal of the treatment? (please specify)</td>
<td>A7  Survival benefit (n = 9), satisfaction of the patients (n = 3)</td>
</tr>
<tr>
<td>Q8  What is the basis for the treatment? (please specify)</td>
<td>A8  Possible to cure HCC (n = 6), to prevent rupture (n = 9), to prevent vascular invasion (n = 5)</td>
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<td>Q9  How do you treat these patients?</td>
<td>A9  Radiofrequency ablation (n = 7), percutaneous ethanol injection therapy (n = 5), TACE (n = 7), hepatic arterial chemotherapy (n = 4), continuous hepatic arterial chemotherapy (n = 4), laparoscopic hepatectomy (n = 1)</td>
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liver function by therapies as a minimum requirement were made by the panelists in the questionnaire.

In terms of treatment modalities, a wide variety of treatments, except for open surgery, were selected in the questionnaire. Unexpectedly, TACE was selected by 7 panelists, whereas only 1 panelist selected blunt embolization. The majority of panelists considered that the beneficial effects of anticancer drugs might exceed their damaging effects on liver function.

Table 2. Summary of findings presented at the workshop

- Many patients with CP-C HCC receive interventional treatments in Japan.
- Some patients benefit from interventions for CP-C HCC.
- Most patients are treated for reasons of survival benefit but seldom for patient satisfaction alone.
- Prevention of HCC perforation and avoidance of major vessel obstruction are two major reasons to treat patients.
- Bridging therapy to liver transplantation is another reason.
- Patients with extremely poor liver function and/or advanced HCC are rarely treated.
- Note that antiviral therapies sometimes improve liver function to CP-B.

Future Directions

While the effects of interventional therapies for CP-C HCC were debated, the consensus obtained in this workshop was that there are certain patients who benefit from the interventions. However, all results were obtained via retrospective observations, and no clear evidence was presented. Recent developments in antiviral therapies that improve liver function are other important considerations. Although there are many uncertainties, this workshop revealed the present status of CP-C HCC treatments in Japan and provided a chance to reconsider treatment options for these difficult-to-treat patients. A summary of the workshop’s findings is provided in Table 2. Future prospective studies are mandatory to clarify optimal treatments for these patients.

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of this article.

References


