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ORIGINAL RESEARCH ARTICLE

Cabozantinib for Advanced Hepatocellular Carcinoma in the Latest Real-World Practice: A Multicenter Retrospective Analysis

Hiroaki Kanzaki[1] · Sadahisa Ogasawara[1] · Tomomi Okubo[2] · Norio Itokawa[2,3] · Ryohei Yoshino[1] · Kentaro Fujimoto[1] · Tadayoshi Kogure[1] · Sae Yumita[1] · Takamasa Ishino[1] · Keita Ogawa[1] · Terunao Iwanaga[1] · Miyuki Nakagawa[1] · Kisako Fujiwara[1] · Ryuta Kojima[1] · Keisuke Koroki[1] · Masanori Inoue[1] · Kazufumi Kobayashi[1] · Naoya Kanogawa[1] · Soichiro Kiyono[1] · Masato Nakamura[1] · Takayuki Kondo[1] · Ryo Nakagawa[1] · Shingo Nakamoto[1] · Ryosuke Muroyama[4] · Ei Itobayashi[5] · Masanori Atsukawa[2,3] · Jun Kato[1] · Naoya Kato[1]

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Abstract

Background Cabozantinib was found to be effective as a second- or third-line treatment after sorafenib in patients with advanced hepatocellular carcinoma (HCC) in the phase 3 CELESTIAL trial. So far, as immunotherapy has substituted molecular target agents as the primary systemic therapy for advanced HCC, cabozantinib is extensively used in the latest real-world clinical practice in a greatly different position than that shown by the CELESTIAL trial. In the current analysis, we examined the safety and effectiveness of cabozantinib administration in real-life settings for patients with advanced HCC.

Methods We retrospectively obtained data from patients with advanced HCC who received cabozantinib in three institutions in Japan between 14 September 2018 and 30 November 2021.

Results During the study period, 23 patients with advanced HCC received cabozantinib. Our cohort included 21.7% of patients with Child–Pugh class B, and 52.2% of patients in fourth line or later. The median progression-free survival of patients given cabozantinib was 3.7 months. Regarding patients with Child–Pugh class B or administration in fourth line or later, the discontinuation rate due to adverse events in patients who initialized at 40 or 20 mg was lower than those who initialized at 60 mg (42.9% versus 75.0%). Patients who were able to continue treatment with cabozantinib for more than 3 months were more likely to undergo dose reduction than those who did not (85.7% versus 25.0%).

Conclusions Cabozantinib has recently been administered to a diverse range of patients, including those who were not enrolled in the CELESTIAL trial. Deliberate dose reduction could potentially offer clinical benefits to patients with impaired liver function. Furthermore, managing adverse events by reducing the dose could play a crucial role in extending the duration of treatment with cabozantinib.

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Hiroaki Kanzaki and Sadahisa Ogasawara contributed equally to this work.

✉ Sadahisa Ogasawara
ogasawaras@chiba-u.jp

1 Department of Gastroenterology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, Japan

2 Department of Gastroenterology, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Japan

3 Division of Gastroenterology and Hepatology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan

4 Department of Molecular Virology, Graduate School of Medicine, Chiba University, Chiba, Japan

5 Department of Gastroenterology, Asahi General Hospital, Asahi, Japan

Key Points

In the latest real-world clinical practice, Cabozantinib is often administered for advanced hepatocellular carcinoma patients, encompassing various patient populations, in contrast to the findings from the CELESTIAL trial.

The use of cabozantinib may provide clinical benefits to patients with advanced hepatocellular carcinoma and compromised liver function by intentionally reducing the dose.

Managing adverse events by reducing the dose of cabozantinib may play a critical role in extending the duration of treatment.

1 Introduction

Primary liver cancer is the sixth most prevalently diagnosed cancer and the fourth highest cause of cancer deaths globally, and hepatocellular carcinoma (HCC) is the most prevalent malignant primary liver cancer [1]. Monitoring high-risk populations, such as patients with chronic hepatitis and cirrhosis due to hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol consumption, and metabolic syndrome, has increased the early diagnosis of patients with HCC [2–4]. However, numerous HCC patients are diagnosed at heightened stages and their long-term survival remains poor, with a 5 year survival rate of less than 20% [5, 6].

1.1 Current Role of Cabozantinib in Advanced Hepatocellular Carcinoma

The landscape of systemic therapy options for advanced HCC has been fast growing and changing rapidly for over a decade. While sorafenib was the only optional systemic therapy for advanced HCC for several years after its implementation in 2007 [7, 8], several agents became available in the late 2010s after exhibiting efficacy in randomized clinical trials in both first- and second-line patients with advanced HCC. Lenvatinib was noninferior to sorafenib in the first-line setting, and regorafenib, cabozantinib, and ramucirumab indicated significantly enhanced survival than placebo as a second-line setting [9–12]. As the first combination immunotherapy in advanced HCC, atezolizumab plus bevacizumab indicated superiority to sorafenib in both overall survival (OS) and progression-free survival (PFS) [13]. Furthermore, durvalumab plus tremelimumab showed considerably prolonged OS than sorafenib treatment in patients with advanced HCC [14]. Nowadays, two combination immunotherapy regimens and five molecular target agents (MTAs) were found to be effective against advanced HCC in global phase 3 randomized control trials and an extensive variety of sequential treatments are being created for clinical practice [7–14].

Cabozantinib is a multikinase inhibitor to control many biological processes such as cellular proliferation, differentiation, and angiogenesis, including MET, VEGFR-2, and AXL [15]. The phase 3 CELESTIAL trial, which was implemented at the time when sorafenib was the only standard front-line agent and before immunotherapy was developed, indicated that cabozantinib was superior to placebo with both OS and PFS in advanced HCC patients who failed one or more systemic chemotherapy regimens, including sorafenib [11]. Based on the CELESTIAL trial, cabozantinib was authorized for second-line systemic therapy for advanced HCC.

However, as stated above, immunotherapy has substituted MTAs as the primary systemic therapy for advanced HCC. Furthermore, several MTAs and one anti-VEGF-R2 antibody could be the treatment option for the second line or later. In other words, cabozantinib is often applied in the latest real-world clinical practice in a significantly different position than that demonstrated by the CELESTIAL trial. With the repositioning of existing agents due to the rapid growth of systemic therapy for advanced HCC, there is still no data on the current safety and efficacy of cabozantinib under the latest real-world clinical practice. The present study sought to assess the safety and efficacy of cabozantinib administration in a real-life setting for patients with advanced HCC.

2 Methods

2.1 Study Design and Selection of Patients

We retrospectively obtained data from patients with advanced HCC who received cabozantinib in three institutions in Japan between 14 September 2018 and 30 November 2021. Data were locked on 28 February 2022. The present study was authorized by the Research Ethics Committee of the Graduate School of Medicine, Chiba University (no. 3091). We had access to information that could recognize individual patients during or after data collection. Patient data were anonymized and deidentified before analysis.

2.2 Treatment with Cabozantinib

The proposed starting dose for cabozantinib in HCC is 60 mg orally once per day. However, patients were allowed to use the initializing dose of 40 or 20 mg orally once per day to maintain performance status, adequate bone marrow, and both liver and renal functioning by the decision of HCC treatment specialists. Dose reductions or interruptions were made based on toxicity and were recommended as 40 or 20 mg, as given in the summary of product characteristics. We applied dynamic contrast-enhanced computed tomography or magnetic resonance imaging at baseline and every 1–2 months after initializing treatment for the assessment of tumor response. Cabozantinib was administered until the physician ascertained a clear progression of disease on radiological imaging or until the incidence of adverse events (AEs) inhibited the continuation of treatment.

2.3 Clinical Parameters

Clinical parameters acquired for this analysis were as follows: baseline demographic data (e.g., sex, age, etc.), etiology, Child–Pugh class, alpha-fetoprotein, radiological assessment, Eastern Cooperative Oncology Group performance status, and Barcelona Clinic liver cancer stage.

Radiological assessments were examined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [19]. Separately, the Common Terminology Criteria for Adverse Events version 5.0 established by the National Cancer Institute was employed to assess AEs.

2.4 Statistical Analysis

Kaplan–Meier plots of medians with 95% confidence intervals (CIs) were used for calculating OS. The censoring date was described as the date of the previous follow-up. PFS after cabozantinib was determined using Kaplan–Meier plots of medians with 95% CIs, with the date of progression described as the date of the last radiological assessment without progression. Time-to-treatment-failure (TTF) after cabozantinib was determined using Kaplan–Meier plots, which displayed medians with 95% CIs. The date of treatment failure was considered as the date when the treatment was discontinued for any reason, such as disease progression, discontinuation due to AEs, or death. We used the log-rank test to assess the statistical significance of the differences in OS, PFS, and TTF.

The level of significance was set as $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences version 25 statistical software (SPSS, IBM, Armonk, NY, USA).

3 Results

3.1 Baseline Characteristics of the Study Population

During the study period, 23 patients with advanced HCC collected cabozantinib at three Japanese institutions. The baseline characteristics of 23 patients are outlined in Table 1. The median age was 73 years (range, 52–84 years). Most of the etiology was HCV ($n = 7$, 30.4%), followed by HBV ($n = 6$, 26.0%) and alcohol abuse ($n = 5$, 21.7%). At the time of cabozantinib administration, most of the patients were Child–Pugh class A ($n = 18$, 78.3%), whereas five (21.7%) were Child–Pugh class B. At the baseline radiological assessments, 5 patients (21.7%) and 15 patients (65.2%) of patients were observed to have macrovascular invasion and extrahepatic metastasis, respectively. Five patients (21.7%) had received sorafenib ($n = 2$, 8.7%) or lenvatinib ($n = 3$, 13.0%) before cabozantinib treatment. Six patients (26.0%) had acquired 2 systemic therapy lines before initiation of cabozantinib and 12 (52.2%) patients had at least 3 prior therapy lines, respectively. Thirteen patients (56.5%) had been treated with atezolizumab plus bevacizumab prior to receiving cabozantinib.

Table 1 Baseline characteristics of 23 patients with hepatocellular carcinoma treated with cabozantinib

Demographics/characteristics	Patients
Gender, male, *n* (%)	18 (78.3)
Age, > 73 years, *n* (%)	13 (56.5)
HBV positive, *n* (%)	6 (26.1)
HCV positive, *n* (%)	7 (30.4)
Alcohol abuse, *n* (%)	5 (21.7)
NAFLD (clinically diagnosed), *n* (%)	2 (8.8)
Child–Pugh class	
A, *n* (%)	18 (78.3)
B, *n* (%)	5 (21.7)
MVI, *n* (%)	5 (21.7)
EHM, *n* (%)	15 (65.2)
BCLC stage C, *n* (%)	16 (69.6)
AFP, > 400 ng/mL, *n* (%)	10 (43.5)
Previous systemic treatment lines	
1, *n* (%)	5 (21.7)
2, *n* (%)	6 (26.1)
≥ 3, *n* (%)	12 (52.2)

HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; MVI, macrovascular invasion; EHM, extrahepatic metastasis; BCLC, Barcelona Clinic liver cancer; AFP, alfafetoprotein

3.2 Efficacy of the Whole Population of the Present Study

At the cutoff date, the median observation period was 3.5 months (95% CI 2.0–6.2 months) and 22 patients (95.6%) had quit cabozantinib. Discontinued rates due to disease progression and AE were 47.8% (11 patients) and 47.8% (11 patients), respectively. The median duration of treatment with cabozantinib was 1.8 months (95% CI 1.0–3.3 months). Overall, 18 patients (78.2%) had at least one follow-up imaging and these patients could be evaluated for tumor response. According to RECIST 1.1, none of the assessed patients indicated a complete response, 1 patient (4.4%) had a partial response, 12 patients (52.2%) indicated stable disease, and 5 patients (21.7%) had progressive disease, respectively. Taken together, we detected an overall response rate (ORR) of 4.4% and a disease control rate (DCR) of 56.6%. The median PFS and OS were 3.7 months (95% CI 1.5–8.9 months) and 4.3 months (95% CI 2.1–8.8 months), respectively (Table 2). When comparing the outcomes based on liver function, patients initiated in Child–Pugh class A had a median PFS of 9.2 months (95% CI 0–20.5 months), whereas those in Child–Pugh class B had a PFS of 0.5 months (95% CI not applicable) ($p = 0.001$). Similarly, the median OS for patients in Child–Pugh class A was 6.9 months (95% CI 3.3–10.5 months), while for those in Child–Pugh class B, it was 2.1 months (95% CI

Table 2 Radiological response and survival data according to the RECIST 1.1 in our study population

Parameter	Patients
Best overall response	
CR, *n* (%)	0
PR, *n* (%)	1 (4.4)
SD, *n* (%)	12 (52.2)
PD, *n* (%)	5 (21.7)
NE, *n* (%)	5 (21.7)
ORR, %	4.4
DCR, %	56.6
PFS, median months (95% CI)	3.7 (1.5–8.9)
OS, median months (95% CI)	4.3 (2.1–8.8)

RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival

0–5.6 months) ($p < 0.001$). Furthermore, the median TTF for patients in Child–Pugh class A was 2.1 months (95% CI 1.9–2.2 months), and for those in Child–Pugh class B, it was 0.5 months (95% CI 0.2–0.7 months) ($p < 0.001$). When comparing based on the treatment lines of cabozantinib, patients administered in the third line or earlier had a median PFS of 9.2 months (95% CI 2.6–15.9 months), whereas those administered in the fourth line or later had a median PFS of 3.7 months (95% CI not applicable) ($p = 0.148$). Similarly, the median OS for patients administered in the third line or earlier was 3.2 months (95% CI 0–19.3 months), while for those administered in the fourth line or later, it was 4.3 months (95% CI 1.2–7.3 months) ($p = 0.708$). Furthermore, the median TTF for patients administered in the third line or earlier was 2.1 months (95% CI 1.5–2.6 months), and for those administered in the fourth line or later, it was 1.1 months (95% CI 0–2.9 months) ($p = 0.144$).

3.3 Safety of the Whole Population of the Present Study

The occurrence of cabozantinib-related AEs is presented in Table 3. AEs of any grade and grade 3 or higher notwithstanding causality were observed in 100% and 56.5% of the patients in our cohort, respectively. The most frequently occurring AEs were aspartate aminotransferase increased (17 patients, 73.9%), increased alanine aminotransferase (15 patients, 65.2%), hypoalbuminemia (12 patients, 52.2%), thrombocytopenia (11 patients, 47.8%), and fatigue (11 patients, 47.8%). The most prevalent grade 3 or higher AEs were palmar-plantar erythrodysesthesia (3 patients, 13.1%), thrombocytopenia (2 patients, 8.7%), hypertension (2 patients, 8.7%), proteinuria (2 patients, 8.7%), and anemia (2 patients, 8.7%).

Table 3 Adverse events during treatment with cabozantinib in our study population

Events	Any grade (%)	Grade ≥ 3 (%)
Any adverse event	23 (100)	13 (56.5)
Aspartate aminotransferase increased	17 (73.9)	1 (4.4)
Alanine aminotransferase increased	15 (65.2)	1 (4.4)
Hypoalbuminemia	12 (52.2)	1 (4.4)
Thrombocytopenia	11 (47.8)	2 (8.7)
Fatigue	11 (47.8)	0
Hypertension	10 (43.5)	2 (8.7)
Anorexia	10 (43.5)	1 (4.4)
Proteinuria	7 (30.4)	2 (8.7)
Diarrhea	7 (30.4)	1 (4.4)
Palmar-plantar erythrodysesthesia	6 (26.1)	3 (13.1)
Anemia	5 (21.7)	2 (8.7)
Rash	4 (17.4)	1 (4.4)
Bilirubin increased	4 (17.4)	1 (4.4)
Hoarseness	4 (17.4)	0
Serum amylase increased	3 (13.1)	0
Hypothyroidism	1 (4.4)	0

Table 4 Drug dosing intensity and modification in our study population

Parameter	Patients
Initial dose	
60 mg, *n* (%)	15 (65.2)
40 mg, *n* (%)	1 (4.4)
20 mg, *n* (%)	7 (30.4)
Patients with a dose reduction due to an AE, *n* (%)	10 (43.5)
Patients with a drug interruption due to an AE, *n* (%)	13 (56.5)
Patients with discontinuation due to an AE, *n* (%)	11 (47.8)
The median duration of drug exposure, months (95% CI)	1.4 (0.8–2.5)
Median average daily dose, mg (95% CI)	22.9 (12.8–40.8)

AE, adverse event

Table 4 highlights drug dosing intensity and modification in our study population. The prescribed starting dose of cabozantinib in patients with HCC is 60 mg. In our cohort, 15 patients (65.2%) received 60 mg of cabozantinib, whereas 1 patient (4.4%) started with 40 mg and 7 patients (30.4%) had 20 mg as an initial dose. Ten patients (43.5%) had dose reductions, 13 patients (56.5%) had drug interruption, and 11 patients (47.8%) had discontinuation due to AEs. The most prevalent facilitators of dose reduction and drug interruption were proteinuria ($n = 4$, 17.4%) and diarrhea ($n = 4$,

17.4%). The most prevalent cause of discontinuation due to AEs was proteinuria ($n = 4$, 17.4%). The median duration of drug exposure with cabozantinib was 1.4 months (95% CI 0.8–2.5 months) and the median average daily dose was 22.9 mg (95% CI 12.8–40.8 mg).

We divided the study population into two groups: patients with Child–Pugh class A and second- or third-line treatment with cabozantinib who met the inclusion criteria for the CELESTIAL trial (group A, $n = 8$) and patients who did not meet the inclusion criteria for the CELESTIAL trial (group B; patients who received cabozantinib for Child–Pugh class B or after fourth-line treatment, $n = 15$). Figure 1 depicts the clinical course of cabozantinib in the two groups. In group A, 12.5% of patients began at 40 or 20 mg as the initial dose, and 46.6% of patients were in group B. The discontinuation rate due to AEs was 25.0% in group A and 60.0% in group B. Focusing on the starting dose in group B, 75.0% of patients who began at 60 mg experienced discontinuation due to AEs, and 42.9% of patients who initialized at 40 or 20 mg experienced discontinuation due to AEs. The median average daily doses were 22.8 mg for group A and 22.9 mg for group B. We also analyzed the patients according to the albumin bilirubin (ALBI) grade [20], but no additional insights were obtained compared with those stratified according to the Child–Pugh class (data not shown).

Finally, we investigated the factors that allowed for long-term treatment with cabozantinib while minimizing treatment discontinuation due to AEs. Initially, the patients in our study were categorized into two groups based on their ability to sustain cabozantinib treatment for a minimum of 3 months. Out of the seven (30.4%) patients who were able to continue cabozantinib for at least 3 months, none belonged to Child–Pugh class B at the beginning of the treatment, and 57.1% had initiated cabozantinib as a second- or third-line therapy. Although all of these patients started cabozantinib at a dose of 60 mg, 85.7% required a dose reduction. However, 28.6% of patients discontinued the treatment due to AEs.

4 Discussion

We assessed the safety and effectiveness of cabozantinib administration for patients with advanced HCC in real-life settings using a retrospective cohort. Cabozantinib was authorized as second-line therapy based on the CELESTIAL trial [11], which recruited only patients with

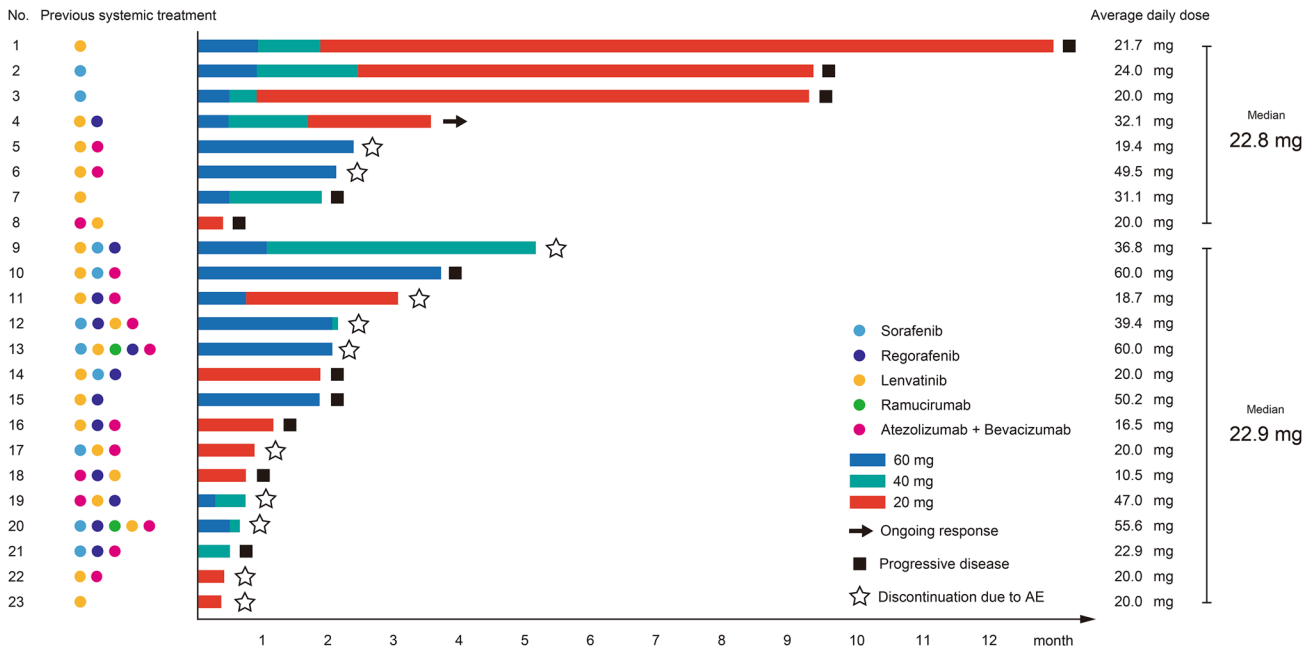

Fig. 1 The clinical course of cabozantinib in the two groups. We categorized the patients into two groups: Child–Pugh class A and administration in third line or earlier (group A, $n = 8$, no. 1–8) and Child–Pugh class B or administration in fourth line or later (group B, $n = 15$, no. 9–23). The duration of cabozantinib in each patient is represented by a bar, along with the daily doses, sorted by the duration of treatment in each group. In group A, 12.5% of patients initialized at 40 or 20 mg dose, and 46.6% of patients in group B. The discontinuation rate due to AEs was 25.0% in group A and 60.0% in group B. Focusing on the starting dose in group B, 75.0% of patients who began at 60 mg experienced discontinuation due to AEs, and 42.9% of patients who started at 40 or 20 mg experienced discontinuation due to AEs. The median average daily doses were 22.8 mg for group A and 22.9 mg for group B

Child–Pugh class A and mainly patients in second-line treatment before the approval of immunotherapy. However, in clinical practice, cabozantinib has been administered to several patients with advanced HCC. The outcomes of the current study indicate cabozantinib has real-life potential in the treatment of advanced HCC, where immunotherapy is the major treatment.

In the era of immunotherapy, cabozantinib might be prevalently administered to patients with poor liver function or at a late line. In our cohort, 21.7% of patients were treated in Child–Pugh class B, and 52.2% of patients were treated in the fourth line or later. Initiation in patients with poor liver function and late-line initiation were more common, but the ORR was 4.4%, DCR was 56.6%, and the median PFS was 3.7 months, similar to the findings of the CELESTIAL trial [11]. These findings were also comparable to those of a recent multicenter retrospective study (ORR, 3.6–6.8%; DCR, 38.6–66.3%; median PFS, 3.2–5.1 months) [16–18].

Although cabozantinib might be clinically beneficial in difficult-to-treat patient populations, another very critical point is to administer it while avoiding discontinuation due to AEs. Despite the inclusion of patients with poor liver function or at the late line, 56.5% of AEs of grade 3 or higher were detected, irrespective of causality, and these outcomes were similar to those of the CELESTIAL trial [11]. In our cohort, 15 patients (65.2%) received 60 mg of cabozantinib, whereas 1 patient (4.4%) started with 40 mg and 7 patients (30.4%) had 20 mg as the initial dose, and we presume that this change in starting dose was a key reason for its application while avoiding discontinuations due to AEs. Indeed, we segmented our cohort into two groups: patients with Child–Pugh class A and who received second- or third-line treatment with cabozantinib and met the inclusion criteria for the CELESTIAL study (group A) and patients who did not meet the inclusion criteria for the CELESTIAL study (group B). Then, we evaluated comprehensively the course of oral administration in each group. Focusing on the starting dose in group B, there were fewer discontinuations due to AEs in patients who initialized at 40 or 20 mg, unlike those who started at 60 mg (42.9% versus 75.0%). The analysis according to ALBI grade showed similar findings. A recent study by Tomonari T et al. suggested that considering a reduced dose of cabozantinib based on the patients' condition should be part of clinical practice [21].

Furthermore, our results indicate that the clinical benefit can be improved by flexibly modifying the dose of cabozantinib, both before and during treatment. Patients who were able to continue treatment with cabozantinib for more than 3 months were more likely to have their cabozantinib dose reduced compared with those who did not (85.7% versus 25.0%). Managing AEs through dose modification of cabozantinib could be the key to extending the duration of treatment.

The clinical course of systemic therapy in patients with advanced HCC primarily starts with combined immunotherapy, followed by sequencing of MTAs [22]. Many MTAs, when utilized in late-line settings, have been found to have reduced therapeutic efficacy and a high AE discontinuation rate [23, 24]. Cabozantinib could be a promising choice, as it has demonstrated sufficient effectiveness in enhancing the chances of long-term treatment through careful initiation of dose reduction and subsequent dose adjustments during treatment.

This study had several limitations that require attention. Firstly, the clinical data in this study were collected retrospectively. Secondly, the sample size in this study was inadequate for conducting accurate analyses, especially in subgroup comparisons. It is important to note that the data were obtained from Japan, a region with a substantial elderly population and a distinct medical insurance system compared with other countries. To elucidate the role of cabozantinib in an era where combined immunotherapy is the primary approach for HCC treatment, a global prospective study should be designed to validate the safety and efficacy of cabozantinib.

5 Conclusions

The latest real-world clinical practice has shown that cabozantinib is commonly prescribed to patients with advanced HCC across various patient populations, unlike the findings from the CELESTIAL trial. In patients with impaired liver function, initiating dose reduction could potentially offer clinical advantages. Effectively managing AE through dose reduction may also play a critical role in extending the duration of treatment with cabozantinib.

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Declarations

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Data Availability All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Approval All procedures performed in this study involving human participants were conducted following the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Formal consent by written signature was not required for this type of study based on Japanese regulations. The Chiba University Research Ethics Committee also approved this point. The Chiba University Research Ethics Committee approved this study (No. 3091).

Consent to Participate An opt-out approach was used to obtain patient-informed consent for publication.

Consent to Publish An opt-out approach was used to obtain patient-informed consent for publication.

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