Factors Contributing to the Prognosis after Second-line Therapy with Ramucirumab in Advanced Hepatocellular Carcinoma

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Abstract:
Objective  Multiple therapeutic agents exist for advanced hepatocellular carcinoma (HCC), but prognostic factors in second-line and subsequent therapies are unclear. Ramucirumab is a molecular-targeted agent effective against hepatocytes with alpha-fetoprotein (AFP) >400 ng/mL after sorafenib failure. We examined the prognostic factors and efficacy of ramucirumab with prior therapy other than sorafenib.

Methods  In our retrospective multicenter study, 33 patients were treated with ramucirumab for HCC with prior therapy other than sorafenib, including 1 patient who received 2 lines of ramucirumab. We analyzed background factors, liver reserve, the prognosis, and treatment duration and efficacy.

Results  The median albumin-bilirubin (ALBI) value showed little change during ramucirumab treatment. The ALBI value improved in 32% of patients, and their prognoses were better than in those who did not improve. Response and efficacy rates were not as high as those in the REACH-2 study but were similar when limited to patients with 2,500 ng/mL AFP. Thirteen patients received further treatment after ramucirumab failure and they had a significantly better prognosis from ramucirumab administration and also had a significantly better prognosis from the start of the first tyrosine kinase inhibitor than who did not received further treatment. In univariate and multivariate analyses of prognostic factors, the continuation of treatment with another drug after ramucirumab failure and a good ALBI value at initiation were significant. The presence of a ramucirumab response and treatment duration were not associated with the prognosis. A good ALBI value at initiation and ALBI value improvement during treatment were also identified as independent factors associated with eligibility for further treatment after ramucirumab failure. The treatment line did not correlate with the availability of treatment with another drug after treatment failure.

Conclusions  ALBI value improvement with ramucirumab treatment allows for subsequent treatment after failure and an improved overall prognosis.

Key words: ramucirumab, hepatocellular carcinoma, ALBI value improvement, subsequent treatment

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Introduction

Hepatocellular carcinoma (HCC) is the fourth-most common cause of death among cancers worldwide (1). In recent years, several systemic chemotherapy regimens for HCC have been developed. These include tyrosine kinase inhibitors (TKIs), molecular-targeted agents (MTAs), and immune checkpoint inhibitors (ICIs). Sorafenib was the first TKI to be developed (2, 3), and many subsequent agents have been compared with sorafenib or developed for HCC after sorafenib failure.

Ramucirumab is a recombinant monoclonal human immune globulin (Ig) G antibody-specific inhibitor of vascular endothelial growth factor 2 (VEGFR-2) that has been shown to be effective for the treatment of HCC after the failure of sorafenib. In the REACH-2 study, ramucirumab significantly improved the overall survival (OS) (8.5 months vs. 7.3 months) and progression-free survival (PFS) (1.6 months vs. 2.8 months) compared with placebo in patients with HCC with α-fetoprotein (AFP) >400 ng/mL after sorafenib failure (4). However, in addition to sorafenib and ramucirumab, other MTAs have been developed for HCC, such as lenvatinib (5), regorafenib (6), cabozantinib (7), and atezolizumab plus bevacizumab (8), an immune checkpoint inhibitor that can be used in combination with MTAs. Despite the advent of these various therapies, data are insufficient at present to determine how best to use the various drugs to achieve a better prognosis.

Although analyses of various factors have helped improve the prognosis with first-line treatment (9), few studies have examined the prognosis after second-line treatment. Data from trials on ramucirumab administered after sorafenib and several studies on the effect of ramucirumab after lenvatinib on the safety and efficacy have been reported, but no detailed study has shown patients to have a better prognosis. It is important to investigate which patients will benefit from ramucirumab.

In this multicenter study, we investigated the efficacy and safety of ramucirumab in patients with previously treated HCC to determine the clinical profile with the best prognosis.

Materials and Methods

Patients

Of 298 patients with HCC who were treated at multiple institutions, 33 received ramucirumab between July 2019 and November 2021 and consented to the study before treatment initiation. All patients had been treated with TKIs other than sorafenib, including one patient who had been treated twice. A retrospective analysis was performed on these 32 cases and 33 treatments. This study was approved by the ethics committee of Kyushu Cancer Center (2018-16) and was performed in compliance with the 1975 Declaration of Helsinki.

Clinicopathological features

We investigated the clinicopathological features of patients, including the age, sex, cause of liver disease [hepatitis B virus (HBV), hepatitis C virus (HCV), non-hepatitis B virus, non-hepatitis C virus (NBNC)], type and number of lines of TKIs used before ramucirumab, treatment history, tumor-node metastasis classification (TNM) and Barcelona Clinic Liver Cancer (BCLC) stages, AFP, protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels, total bilirubin level, albumin level, transaminase level, platelet count, tumor size and number, macrovascular invasion, extrahepatic metastasis at the start of treatment, time since the first TKI treatment for HCC, changes in liver reserve at the start of treatment and during treatment, side effects during treatment, and treatment after ramucirumab failure. HBs antigen-positive patients were defined as hepatitis B-derived liver cancer, and HCV antibody-positive patients were defined as HCV-derived liver cancer. HBs antigen-negative and HCV antibody-negative patients were defined as NBNC liver cancer. The treatment response, PFS, time to treatment failure (TTF), and OS were also analyzed retrospectively.

The diagnosis of HCC

A diagnosis of HCC was based on the results of contrast-enhanced computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) at each institution. The clinical stage was expressed using the BCLC stage (10) and TMN stage (11).

The liver function

The liver function was assessed using the Child-Pugh score (12) and ALBI score, calculated using albumin and bilirubin, as follows (13, 14): \[\text{ALBI score} = \log_{10} \text{bilirubin (μmol/L)×0.66} + \text{albumin (g/L)×−0.085}\]. ALBI grades were defined as follows: ALBI grade 1, ≤−2.60; ALBI grade 2, >−2.60 to ≤−1.39; and ALBI grade 3, >−1.39. To further subdivide moderate liver injury, modified albumin-bilirubin (mALBI) grades were classified as 1, 2a, 2b, and 3, as follows: mALBI grade 1, ≤−2.60; mALBI grade 2a, >−2.60 to ≤−2.270; mALBI grade 2b, >−2.270 to ≤−1.39; and mALBI grade 3, >−1.39 (14).

Adverse effect determination

Adverse effects associated with ramucirumab treatment were determined based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The most severe grade that occurred during the observation period was noted.

Statistical analyses

Data were expressed as the mean and standard deviation. Statistical analyses were performed using Welch’s t-test, Student’s t-test, Fisher’s exact test, Mann-Whitney U-test, Cox’s hazard analysis, a Kaplan-Meier analysis, a logistic analysis,
Table 1. Baseline Characteristics and Previous TKI Data.

| Overall (n=33) |
|----------------|
| **Age, years** | 75 (68-79) |
| **Male sex**   | 26 (79)    |
| **Child-Pugh score** |
| A5             | 10 (30)    |
| A6             | 15 (45)    |
| B7             | 5 (15)     |
| B8             | 3 (10)     |
| **ALBI grade** |
| 1              | 11 (33)    |
| 2a             | 6 (18)     |
| 2b             | 15 (45)    |
| 3              | 1 (4)      |
| **BCLC**       |
| B              | 13 (39)    |
| C              | 20 (61)    |
| **TMN stage of LCSGJ 6th** |
| III            | 11 (33)    |
| IVa            | 6 (18)     |
| IVb            | 16 (49)    |
| **Intrahepatic tumor size (mm)** | 38 (29.7-55.5) |
| **Intrahepatic tumor number** |
| 0              | 2 (6)      |
| 1-3            | 4 (12)     |
| 4-10           | 10 (30)    |
| >10            | 17 (52)    |
| **Positive for MVI** | 9 (27) |
| **Positive for EHM** |
| Lung           | 8 (24)     |
| Peritoneal dissemination | 6 (18) |
| LN             | 4 (12)     |
| Bone           | 1 (3)      |
| Others         | 2 (6)      |
| **AFP (ng/mL)** | 2,166 (790-5,261) |
| **PIVKA-II (mAU/mL)** | 1,683.5 (478-10,113) |
| **Total bilirubin (mg/dL)** | 0.7 (0.56-1.0) |
| **Albumin (g/dL)** | 3.6 (3.3-4.0) |
| **AST (IU/L)**  | 39 (33-56) |
| **ALT (IU/L)**  | 38 (20-50) |
| **Platelet×10⁴/µL** | 14.5 (9.6-20.0) |
| **Ramucirumab line** |
| 2st            | 17 (52)    |
| 3rd            | 10 (30)    |
| 4th            | 5 (15)     |
| 6th            | 1 (3)      |
| **Previous TKI therapy** |
| Sorafenib      | 14 (42)    |
| Lenvatinib     | 31 (94)    |
| Regorafenib    | 6 (18)     |
| Cabozantinib   | 2 (6)      |
| Atezolizumab+bevacizumab | 3 (9) |
| **Previous immune checkpoint inhibitor** | 5 (15) |
| **Cause of liver disease** |
| HBV            | 7 (22)     |
| HCV            | 13 (39)    |
| NBNC           | 13 (39)    |

Data are expressed as the median (first-third quartiles) or number (%). Baseline data were determined at the time of ramucirumab initiation.

TKI: tyrosine kinase inhibitor, LCSGJ: Liver Cancer Study Group of Japan, MVI: macrovascular invasion; EHM: extrahepatic metastasis; LN: lymph nodes, BCLC: Barcelona Clinic Liver Cancer, AFP: α-fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonist-II, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HBV: hepatitis B virus, HCV: hepatitis C virus, NBNC: non-hepatitis B virus non-hepatitis C virus

log-rank test, and c-index. All statistical analyses were performed using the JMP Pro software program version 15.1.0 (SAS Institute, Cary, USA), and graphs were generated using the PRISM software program version 9.1.0 (GraphPad Software, La Jolla, USA).

Results

Thirty-three treatment cases (including one case of re-administration) were included in this study. Table 1 presents a list of background factors at the start of treatment. There were more older patients than in the REACH/REACH-2 trial, and approximately 20% of the patients were Child-Pugh grade B. Twenty-seven percent had macrovascular invasion (MVI), and 48% had extrahepatic metastases (EHMs). In half of the cases, there were more than 10 hepatocarcinomas in the liver. The BCLC stage was B in 61%, and the TMN stage was III in 33%, 4a in 18%, and 4b in 52% of cases.

Approximately half of the patients were treated after third-line treatment. All patients had received prior therapy other than sorafenib. The median OS from ramucirumab initiation was 11.1 (9.2-21.7) months. The TTF for ramucirumab was 2.6 (1.8-4.2) months (Fig. 1a, b). The raw data concerning the change in the ALBI value for all patients on ramucirumab treatment are shown in Fig. 2a, and the median value is shown in Fig. 2b. About half of the patients were able to continue ramucirumab treatment until week 6. The ALBI values at the beginning and end of ramucirumab treatment are shown in Fig. 2c. Compared with the start of ramucirumab treatment, the median ALBI value remained relatively unchanged at weeks 2, 4, and 6 and at the end of treatment.

On comparing patients with and without a worsening ALBI value, those without a worsening ALBI value had a significantly better OS than those with a worsening value (16 vs. 9.2 months, p=0.0168) (Fig. 3a). Among these patients without a worsening ALBI value, there were 10 cases in which the ALBI value improved after treatment compared with before treatment. These 10 patients tended to have a longer median survival than those without an improved ALBI value [16 (9.3-21.7) vs. 9.4 (8.2-not reached) months, p=0.0577] (data not shown).

One of these patients was not known to have received further treatment after ramucirumab failure, so only the remaining nine were studied further. Eight of the nine patients were able to receive subsequent treatment after ramucirumab failure (post-treatment), which was significantly more frequent than in patients without improvement (89% vs. 53%, p=0.0474). Approximately half of the patients received post-treatment, including four with lenvatinib (three with further sequential treatment), five with sorafenib (one with further sequential treatment), four with atezolizumab plus bevacizumab, three with transcatheter arterial chemo embolization (TACE) (one with further sequential treatment with atezolizumab plus bevacizumab, one with ramucirumab restarted),
Figure 1. The prognosis of all patients after initiation of ramucirumab and duration of treatment with ramucirumab. a: The overall survival in all cases (n=32); median, 11.1 months [95% confidence interval (CI) 9.23-21.7]. b: Time to treatment failure in all cases (n=33); median, 2.6 months (95% CI; 1.8-4.2)

Figure 2. Changes in ALBI values since the start of ramucirumab treatment. a: ALBI values for all patients receiving ramucirumab treatment. b: Change in the median ALBI value for all patients receiving ramucirumab treatment (at start, week 1, week 2, week 3, week 4, week 5, week 6): at start, -2.4339; week 2, -1.9786; week 4, -2.0905; and week 6, -2.3204. c: ALBI values for all patients receiving ramucirumab treatment (at the start, at the end of treatment).

and one with hepatic arterial infusion chemotherapy (HAIC). The presence or absence of post-treatment was not related to the treatment line. The prognosis from the start of ramucirumab was significantly better in the group with post-treatment than in the group without post-treatment (21.7 vs. 8.4 months) (p=0.0004) (Fig. 3b).

There were no significant differences in the duration of ramucirumab treatment for any of the conditions, including the ALBI value at initiation, Child-Pugh score, line of treatment, age, etiology, number of tumors, maximum tumor diameter, presence of EHM, and presence of MVI. In terms of side effects, the incidence of urinary protein was significantly higher in patients who had urinary protein during the previous treatment than in those who had not had it (90% vs. 10.5%) (p=0.0001) (data not shown). In the 30 patients for whom efficacy could be determined, the overall response rate (ORR) and disease control rate (DCR) using the modified Response Evaluation Criteria in Solid Tumors (mRE-
Figure 3. The prognosis of different conditions after ramucirumab administration. a: ALBI value with exacerbation vs. without exacerbation. A comparison of the survival with and without ALBI value exacerbation. The overall survival (OS) with exacerbation (n=13) was significantly shorter than that without exacerbation (n=17) at 9.2 vs. 16.0 months, respectively (p=0.0168). b: Presence vs. absence of post-treatment after ramucirumab failure. The prognosis from the start of ramucirumab according to the presence of post-treatment after ramucirumab failure. The OS with post-treatment (n=18) was significantly longer than that without post-treatment (n=12) at 21.7 vs. 8.4 months, respectively (p=0.0004).

Table 2. Anti-tumor Effect of Different AFP Levels (mRECIST).

| Evaluation | mRECIST n (%) | mRECIST n (%) |
|------------|--------------|--------------|
|             | AFP <2,500 ng/mL | AFP ≥2,500 ng/mL |
| CR         | 0 (0)         | 1 (7.1)       |
| PR         | 1 (6.3)       | 1 (7.1)       |
| SD         | 3 (18.7)      | 4 (28.5)      |
| PD         | 12 (75.0)     | 8 (57.1)      |

mRECIST: modified Response Evaluation Criteria in Solid Tumors, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, AFP: α-fetoprotein, ORR: overall response rate, DCR: disease control rate.

Table 2 continued.

| Evaluation | mRECIST n (%) | mRECIST n (%) |
|------------|--------------|--------------|
|             | AFP <2,500 ng/mL | AFP ≥2,500 ng/mL |
| ORR         | 6.3          | 14.3         |
| DCR         | 25.0         | 42.8         |

mRECIST: modified Response Evaluation Criteria in Solid Tumors, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, AFP: α-fetoprotein, ORR: overall response rate, DCR: disease control rate.

Factors contributing to the prognostic value of ramucirumab were analyzed (Table 3). One factor contributing to the survival from the start of ramucirumab treatment was extracted in the univariate and multivariate analyses: the administration of subsequent treatment. In addition to an ALBI value of G1 at the time of initiation, univariate and multivariate analyses indicated that ALBI value improvement was an independent factor that contributed to patients being eligible for further treatment after ramucirumab failure (Table 4). The median survival time from the start of TKI was 28.1 months (24.0 months-not reached). An analysis of the
ramucirumab post-treatment and non-ramucirumab post-treatment groups showed that the ramucirumab post-treatment group had a significantly better prognosis than the non-post-treatment group in terms of the survival from the start of TKI (28.2 vs. 22.9 months, p=0.0487) (data not shown).

Discussion

First-line molecular-targeted therapy for HCC includes sorafenib, lenvatinib, and atezolizumab plus bevacizumab, and the second and subsequent lines include regorafenib after failure of sorafenib, ramucirumab for patients with AFP >400 ng/mL, and cabozantinib. One study reported that the prognosis of HCC was improved by the sequential use of these therapeutic agents (15). There have been multiple reports of factors that contribute to the prognosis in first-line treatment, and there was a report that the post-progression survival (PPS), but not the PFS, defined the prognosis of HCC (9). However, no reports have investigated the relationship of the ALBI value with the viability of subsequent treatment after second or subsequent treatment failure. This analysis demonstrated that even after second or subsequent-line treatment, the group with a better ALBI value at the start was significantly more likely to move on to further treatment after subsequent treatment failure. The ALBI value at initiation and improvement in the ALBI value during treatment contributed to the ability to continue treatment after ramucirumab treatment failure. Studies have reported that patients with a good ALBI value at the first-line treatment were more likely to be treated later and have a better long-term prognosis than those with a poor value (16, 17). For second-line treatment, the PFS and OS were better in patients with a better ALBI value than in those with a worse value (18), but there have been no reports on the relationship of the ALBI value with the viability of subsequent treatment after second or subsequent treatment failure. This analysis demonstrated that even after second or subsequent-line treatment, the group with a better ALBI value at the start was significantly more likely to move on to further treatment after subsequent treatment failure. The median ALBI value score did not change significantly from the beginning to the end of ramucirumab treatment. Ramucirumab treatment was characterized by an improvement in the ALBI value during treatment in approximately 30% of cases. Patients with an improved ALBI value tended to have a better prognosis after initiation of ramucirumab than those without an improved value and were also significantly more likely to be able to move on to subsequent treatment after ramucirumab failure. The ALBI value did not worsen in half of the patients, but this group also had a good prognosis with a high likelihood of receiving subsequent treatment. The ALBI value was reported to worsen during treatment with lenvatinib (19) or sorafenib (20) and to not improve with time. An ALBI value improvement in 30% of cases is considered characteristic of ramucirumab treatment.

Regarding ramucirumab treatment, the time to progression (TTP) of treatment after lenvatinib was not as long as that extending the survival.

The good ALBI value at initiation and improvement in the ALBI value during treatment contributed to the ability to continue treatment after ramucirumab treatment failure. Studies have reported that patients with a good ALBI value at the first-line treatment were more likely to be treated later and have a better long-term prognosis than those with a poor value (16, 17). For second-line treatment, the PFS and OS were better in patients with a better ALBI value than in those with a worse value (18), but there have been no reports on the relationship of the ALBI value with the viability of subsequent treatment after second or subsequent treatment failure. This analysis demonstrated that even after second or subsequent-line treatment, the group with a better ALBI value at the start was significantly more likely to move on to further treatment after subsequent treatment failure. The median ALBI value score did not change significantly from the beginning to the end of ramucirumab treatment. Ramucirumab treatment was characterized by an improvement in the ALBI value during treatment in approximately 30% of cases. Patients with an improved ALBI value tended to have a better prognosis after initiation of ramucirumab than those without an improved value and were also significantly more likely to be able to move on to subsequent treatment after ramucirumab failure. The ALBI value did not worsen in half of the patients, but this group also had a good prognosis with a high likelihood of receiving subsequent treatment. The ALBI value was reported to worsen during treatment with lenvatinib (19) or sorafenib (20) and to not improve with time. An ALBI value improvement in 30% of cases is considered characteristic of ramucirumab treatment.

Table 3. Cox Hazard Analysis and Weighted Least-squares Regression Analysis of Characteristics and Prognostic Factors.

| Characteristics | Univariate analysis | Multivariate analysis |
|-----------------|---------------------|----------------------|
|                 | HR (95%CI) | p value | HR (95%CI) | p value |
| ALBI grade at start of ramucirumab (grade 1/2a) | 0.68 (0.20-2.06) | 0.50 | 0.69 (0.20-2.00) | 0.50 |
| Anti-tumor effect (CR+PR) | 0.59 (0.03-3.11) | 0.59 | 0.59 (0.03-3.09) | 0.59 |
| Treatment after ramucirumab failure (yes) | 0.14 (0.04-0.47) | 0.0015* | 0.13 (0.03-0.50) | 0.0028* |
| ALBI improvement during treatment (yes) | 0.27 (0.04-1.08) | 0.065 | 0.23 (0.03-1.04) | 0.0570 |

HR: hazard ratio, CR: complete response, PR: partial response, *: significant difference

Table 4. Analysis of Factors Contributing to the Availability of Post-treatment after Ramucirumab Failure: Logistic Analysis.

| Characteristics | Univariate analysis | Odds ratio (95%CI) | Multivariate analysis | Odds ratio (95%CI) |
|-----------------|---------------------|-------------------|----------------------|-------------------|
| ALBI grade at start of ramucirumab (grade 1/2a) | 0.0021* | 17.28 (2.53-353.1) | 0.0020* | 29.37 (3.08-772.0) |
| Reason for stopping treatment (AE) | 0.2576 | 0.4 (0.07-1.96) | 0.6667 | 0.589 (0.04-7.14) |
| ALBI improvement during treatment (yes) | 0.0474* | 7.2 (1.021-147.4) | 0.0011* | 20.87 (2.06-565.8) |

CI: confidence interval, AFP: α-fetoprotein, CR: complete response, PR: partial response, AE: adverse events, *: significant difference
after sorafenib (21). In this study, all patients had a history of TKI treatment other than sorafenib, and the TTF was as short as 2.8 months in those analyses. However, the duration of ramucirumab treatment did not correlate with the prognosis from the start of ramucirumab treatment or the overall prognosis with a TKI. The results of the REACH-2 study after sorafenib treatment showed a significant correlation between the PFS and OS (22). The relationship between the duration of ramucirumab treatment and the OS in patients who received pretreatment TKIs other than sorafenib has not been clarified. Based on the results of our study, the ORR, PFS, and TTF of ramucirumab treatment with prior therapy other than sorafenib do not appear to be directly related to the prognosis, but an improved ALBI value during ramucirumab treatment and subsequent treatment may contribute to the overall prognosis.

Regarding the therapeutic efficacy, a previous report demonstrated that ramucirumab had a relatively good DCR and ORR, even after lenvatinib (23). Furthermore, the therapeutic effect in the high-AFP group was better than that of sorafenib (24). The DCR of all patients in the present study was poorer than that in the clinical trial (REACH-2 study), but the treatment outcome in the high-AFP group (>2,500 ng/mL) was as good as that in the REACH-2 study (4).

Several limitations associated with the present study warrant mention. First, it was a retrospective observational study and not a randomized study. Second, there were only 33 cases. Even so, this report shows the importance of further treatment in the second and subsequent lines of treatment and underscores the importance of improving and maintaining the ALBI value. It will be important to study additional cases.

Given our experience, while there are many drugs for advanced HCC, it is important to maintain and improve the hepatic reserve and progress to the next treatment in order to improve the overall OS, and ramucirumab is useful for this purpose.

The authors state that they have no Conflict of Interest (COI).

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