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Transient deterioration of albumin–bilirubin scores in early post-dose period of molecular targeted therapies in advanced hepatocellular carcinoma with 50% or higher liver occupation
A STROBE-compliant retrospective observational study

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Abstract

Real-world clinical cases of molecularly targeted agent (MTA) administration to patients with advanced hepatocellular carcinoma (HCC) with ≥50% liver occupation have been reported, but treatment outcomes have rarely been described. We have encountered several cases in which albumin–bilirubin (ALBI) scores deteriorated markedly and C-reactive protein (CRP) levels elevated in the early post-dose period. The present study therefore investigated early clinical changes in ALBI score and CRP levels after initiating MTA in advanced HCC patients with ≥50% liver occupation, focusing on antitumor response at 6 weeks.

This retrospective study included 46 HCC patients with liver occupation ≥50% and 191 patients with <50%, Child-Pugh score ≤7, and Eastern Cooperative Oncology Group Performance Status scores of 0 or 1, who were treated with sorafenib or lenvatinib as first-line systemic therapy at our hospital between June 2011 and January 2020. We analyzed their medical records up to March 2020 and investigated the outcomes and changes in CRP and ALBI scores classified according to antitumor response at 6 weeks.

Overall survival was significantly longer in patients with partial response (PR) + stable disease (SD) (13.7 months) than in patients with progressive disease (PD) (1.7 months, $P < .001$) in the ≥50% group. Patients with antitumor response of PR + SD at 6 weeks in the ≥50% group showed more marked deterioration of ALBI score at 2 weeks than those in the <50% group. These significant differences between groups had again disappeared at 4 and 6 weeks. Focusing on patients with PD at 6 weeks, ALBI score deteriorated over time in both groups. Regarding CRP, on 6-week PR + SD patients, a significant increase in CRP levels at 1 and 2 weeks was evident in the >50% group compared to the <50% group. These significant differences between groups had again disappeared at 4 and 6 weeks. In PD patients, no difference between groups in CRP elevation occurred at 1 and 2 weeks.

In MTA treatment for patients with ≥50% liver occupation, to obtain an antitumor response of PR + SD, adequate management might be important considering transient deteriorated ALBI scores and elevated CRP levels.

Abbreviations: AEs = adverse events, ALBI = albumin–bilirubin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, MTA = molecularly targeted agent, OS = overall survival, PD = progressive disease, PR = partial response, PS = performance status, SD = stable disease, TTP = time to progression.

Keywords: C-reactive protein, hepatocellular carcinoma, lenvatinib, sorafenib, treatment outcome, tumor burden

1. Introduction

The prognosis for hepatocellular carcinoma (HCC) patients with high intrahepatic tumor burden generally remains very poor. A liver occupation rate ≥50% is defined in the Cancer of the Liver Italian Program score as a large tumor burden, and has been included as an independent factor associated with poor prognosis.[1] Transarterial chemoembolization has often been performed for huge HCCs that are ineligible for surgical resection, but has limited effects on patients with large tumor burden.[2] Although transarterial infusion chemotherapy has sometimes been performed in patients for whom transarterial chemoembolization is inappropriate,[3] the prognosis of HCC patients with tumor liver occupancy ≥50% remains particularly poor.[4] No consensus has been reached on treatment for HCC showing ≥50% liver occupation.

In recent years, European Association for the Study of the Liver guidelines has recommended administration of sorafenib for Barcelona Clinic Liver Cancer stage C and stage B HCC unsuitable for locoregional therapies.[5] Many unresectable HCCs with ≥50% liver occupation fall into this category. Although outcomes have not been reported, sorafenib has been used for HCC with ≥50% liver occupation in actual clinical practice. Based on the results of the phase III REFLECT trial, lenvatinib has been clinically available as an effective first-line therapy, along with sorafenib, for advanced unresectable HCC since 2018.[6] However, patients with ≥50% liver occupation, obvious invasion of the bile duct, or invasion at the main portal vein were excluded from the REFLECT study. Few previous reports appear to have described the effects of systemic therapies in patients with ≥50% liver occupation,[7,8] although some patients have been treated with sorafenib or lenvatinib in actual clinical practice. In our experience of sorafenib or lenvatinib therapy for HCC patients with ≥50% liver occupation, we have encountered several cases of patients with markedly elevated levels of C-reactive protein (CRP) and exacerbated liver function during the first 2 weeks post-dose, who nonetheless exhibited good antitumor response. Especially in advanced HCC, switching to a more adequate treatment needs to be performed as early as possible. Several reports have shown that initial response to molecularly targeted agent (MTA) at 4 to 6 weeks after starting treatment is an important predictor for prognosis.[9–11] Even after the combination of atezolizumab and bevacizumab became available as a first-line systemic treatment for unresectable advanced HCC in 2020,[12] sorafenib and lenvatinib have remained important as second-line treatments. The present study therefore examined early clinical changes in CRP levels and albumin–bilirubin (ALBI) score[13] after starting MTA treatment in advanced HCC patients with ≥50% liver occupation compared with <50% liver occupation, focusing on the antitumor response at 6 weeks.

2. Methods

2.1. Patient eligibility

We retrieved the medical records of 259 consecutive patients with advanced HCC started sorafenib or lenvatinib therapy as first-line systemic therapy between June 2011 and January 2020 in our hospital, who were followed up until March 2020. Inclusion criteria were as follows: HCC stage equivalent to Barcelona Clinic Liver Cancer stage B or C; not eligible for surgical resection or locoregional therapy; Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1, and Child-Pugh score ≤ 7. We excluded patients who were not evaluated for antitumor response for any reason (n = 5), started sorafenib treatment at a dose of 200 mg/day for any reason (n = 9), or received additional locoregional treatment within 6 weeks of starting treatment (n = 5; Fig. 1). Finally, the remaining 237 patients were enrolled in this study and underwent retrospective evaluation. In general, sorafenib and lenvatinib are recommended only for patients classed as Child-Pugh A. However, in real-world practice, some patients with Child-Pugh B are treated with sorafenib or lenvatinib under careful management by HCC treatment specialists, when no other effective therapeutic options are available.[14–16] Forty-six patients with ≥50% liver occupation (≥50% group) and 191 patients with <50% liver occupation (<50% group) were enrolled in the present study and underwent retrospective evaluation of outcomes. Patients seen before February 2018 were treated with sorafenib. After March
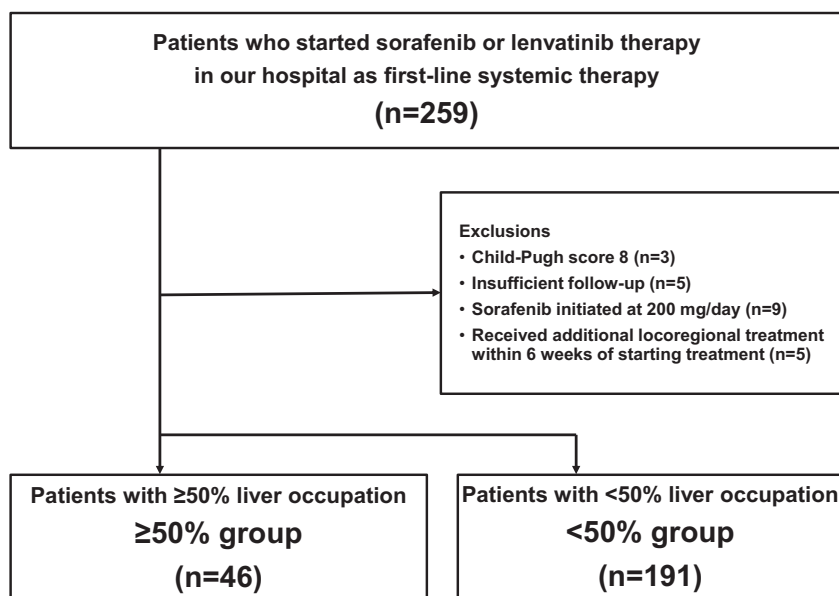

Figure 1. Flowchart of study enrolment.

2018, patients were treated with sorafenib or lenvatinib depending on patient preference.

2.2. Sorafenib or lenvatinib treatment and assessment of adverse events

The starting dose of sorafenib (Nexavar; Bayer Yakuhin, Osaka, Japan) was 800 mg/day administered orally. However, the initial dose of sorafenib was 400 mg/day for patients ≥80 years old, weighing ≤50 kg, with poor renal function, or with a history of treatment for varices or ascites.[11] Lenvatinib (Lenvima; Eisai Co., Tokyo, Japan) was administered orally at a starting dose of 12 mg/day for patients weighing ≥60 kg or 8 mg/day for those weighing <60 kg.[17] Sorafenib or lenvatinib treatment was continued until the occurrence of potentially fatal adverse events (AEs) or clinical tumor progression. AEs were assessed according to the Common Terminology Criteria for Adverse Events version 4.0. If drug-related AEs occurred, dose reduction or temporary interruption was maintained until symptoms resolved to grade 1 or 2, according to the guidelines provided by the manufacturer. For fever, patients who were regularly taking non-steroidal anti-inflammatory drugs were excluded from the analysis.

2.3. Image-based evaluation of antitumor response

Four-phase (i.e., unenhanced, late arterial, portal venous, and equilibrium phase) contrast-enhanced computed tomography examinations were performed at baseline, and at 6 weeks after starting sorafenib or lenvatinib administration.[11,17] Antitumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors.[18]

2.4. Evaluation of changes in liver function and CRP after drug administration

For each patient, ALBI score was calculated at baseline, 1, 2, 4, and 6 weeks after starting drug administration, then ΔALBI was calculated by subtracting the ALBI score at baseline from each value. The formula for ALBI relies on the following equation: ALBI score = (log 10 bilirubin [mg/dL] × 17.1 × 0.66) + (albumin [g/dL] × 10 × −0.0852).[13] ΔCRP was calculated by subtracting the C-reactive protein (CRP) level at baseline from the level at each point.

2.5. Statistical analysis

Statistical analyses were performed using EZR version 1.40 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[19] For continuous variables, differences across groups were compared using the Mann–Whitney U test or Student's t test according to the data type. Categorical variables were analyzed using Fisher's exact probability test. Overall survival (OS), time to progression (TTP), and durations of treatment were calculated using the Kaplan–Meier method, and differences in survival were evaluated by the log-rank test. For all analyses, values of $P < .05$ were considered significant.

2.6. Statement of ethics

This study was approved by the ethics committee at Nagoya University Graduate School of Medicine and was performed in compliance with the 1975 Declaration of Helsinki. The need for informed consent in this retrospective study was considered to have been met in the form of allowing opt-out via the institutional website.

3. Results

3.1. Baseline characteristics of patients

The characteristics of patients are listed in Table 1. Median observation time was 11.5 months (range, 0.5–90.1 months). There were 46 patients in the ≥50% group and 191 patients in the <50% group. Concentrations of alpha-fetoprotein, CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet counts, and white blood cell counts were significantly higher in the ≥50% group. ECOG PS, ALBI score, and Child-Pugh score were significantly worse in the ≥50% groups than in the <50% group.

Table 1

Comparison of characteristics between ≥50% and <50% groups.

Factor	≥50% group (n=46)	<50% group (n=191)	P value
Median age (yr, range)	68 (35–85)	70 (34–92)	.062
Sex (male/female), n (%)	38 (82.6)/8 (17.4)	151 (79.1)/40 (20.9)	.686
Etiology (HBV/HCV/NBNC), n (%)	11 (23.9)/9 (19.6)/26 (56.5)	38 (19.9)/75 (39.3)/78 (40.8)	.033
ECOG PS (0/1), n (%)	24 (52.2)/22 (47.8)	135 (70.7)/56 (29.3)	.023
BCLC stage (B/C), n (%)	4 (8.7)/42 (91.3)	69 (36.1)/122 (63.9)	<.001
Previous treatment (absent/present), n (%)	28 (60.9)/18 (39.1)	24 (12.6)/167 (87.4)	<.001
Child-Pugh score (5/6/7), n (%)	16 (34.8)/20 (43.5)/10 (21.7)	114 (59.7)/64 (33.5)/13 (6.8)	.001
Median ALBI score, (range)	−1.94 (−3.20 to −1.20)	−2.33 (−3.24 to −1.15)	.006
Portal vein invasion (absent/present), n (%)	14 (30.4)/32 (69.6)	147 (77.0)/44 (23.0)	<.001
Distal tumor metastasis (absent/present), n (%)	26 (56.5)/20 (43.5)	122 (63.9)/69 (36.1)	.398
Portal hypertension (absent/present), n (%)	32 (69.6)/14 (30.4)	114 (59.7)/77 (40.3)	.241
Median platelet count, ×10³/μL (range)	234.5 (86–563)	124 (33–479)	<.001
Median hemoglobin count, mg/dL (range)	12.15 (7.90–17.4)	12.7 (8.2–17.3)	.187
Median white blood cell count, /μL (range)	6150 (2800–16,400)	4300 (1500–14,700)	<.001
Median prothrombin time, % (range)	91.75 (45.4–125.6)	90.9 (20.0–116.9)	.622
Median serum CRP, mg/dL (range)	1.60 (0.0–18.0)	0.19 (0.0–12.7)	<0.001
Median serum ALT, IU/L (range)	44.5 (9–262)	30 (7–147)	.002
Median serum AST, IU/L (range)	75.5 (26–592)	40 (12–177)	<.001
Median serum AFP, ng/mL (range)	1512 (2.00–3,610,200)	74 (1–192,466)	<.001
Drug (sorafenib/lenvatinib), n (%)	36 (78.3)/10 (21.7)	152 (80.7)/39 (19.3)	.841

AFP = α-fetoprotein, ALBI score = albumin–bilirubin score, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CRP = C-reactive protein, ECOG PS = Eastern Cooperative Oncology Group performance status, HBV = hepatitis B viral infection, HCV = hepatitis C viral infection, mALBI grade = modified albumin–bilirubin grade, NBNC = non-B-non-C viral hepatitis.

Antitumor response at 6 wk in the ≥50% and <50% groups.

	CR n	PR n	SD n	ORR n (%)	DCR n (%)
≥50% (n=46)	0	11	10	11 (23.9%)	21 (45.7%)
<50% (n=191)	0	43	107	43 (22.5%)	150 (78.5%)
P value				.846	<.01

CR = complete response, DCR = disease control rate, ORR = objective response rate, PR = partial response, SD = stable disease.

3.2. Antitumor responses at 6 weeks, OS, and TTP in the ≥50% and <50% groups

Assessment of antitumor response at 6 weeks using modified Response Evaluation Criteria in Solid Tumors showed complete response, partial response (PR), and stable disease (SD) in 0 (0%), 11 (23.9%), and 14 (30.4%) patients in the ≥50% group and in 0 (0%), 43 (22.5%), and 107 (56.0%) patients in the <50% group, respectively (Table 2). The disease control rate at 6 weeks was significantly lower in the ≥50% group (45.7%) than in the <50% group (78.5%; $P < .001$). Objective response rate at 6 weeks did not differ significantly between groups (23.9% vs 22.5%, $P > .846$). Median OS was significantly shorter in the ≥50% group (4.8 months) than in the <50% group (19.4 months, $P < .001$). Median TTP was also significantly shorter in the ≥50% group (3.0 months) than in the <50% group (5.0 months, $P = .001$). In both the ≥50% group and the <50% group, the cause of death was mostly cancer progression, and there was no significant difference between the 2 groups (90.1% in the ≥50% group and 98.0% in the <50% group, $P = .099$).

3.3. OS of patients with PR + SD and progressive disease (PD) at 6 weeks

In the ≥50% group, OS was significantly longer in patients with PR + SD (13.7 months) than in patients with PD (1.7 months, $P < .001$; Fig. 2a). In the <50% group, OS was significantly longer in patients with PR + SD (22.0 months) than in patients with PD (7.3 months, $P < .001$; Fig. 2b). In addition, PR patients had a significantly prolonged prognosis compared to SD patients in the <50% group, whereas there was no significant difference between them in the ≥50% group (Supplementary Figure 1, http://links.lww.com/MD/G331). Among the baseline characteristics limited to patients with PR + SD, ECOG PS, Child-Pugh score, and ALBI score did not differ significantly between groups, unlike the study of the entire cohort (Supplementary Table 1, http://links.lww.com/MD/G335). The number of patients who received locoregional therapies after the start of MTA is shown in Supplementary Table 2, http://links.lww.com/MD/G336. Two of the patients in the ≥50% group, who had achieved antitumor response of SD + PR, underwent liver resections for curative treatment.

## ≥50% group (n=46)	## <50% group (n=191)

Number at risk

PR + SD	21	3	2	1	1
PD	25	0	0	0	0

Number at risk

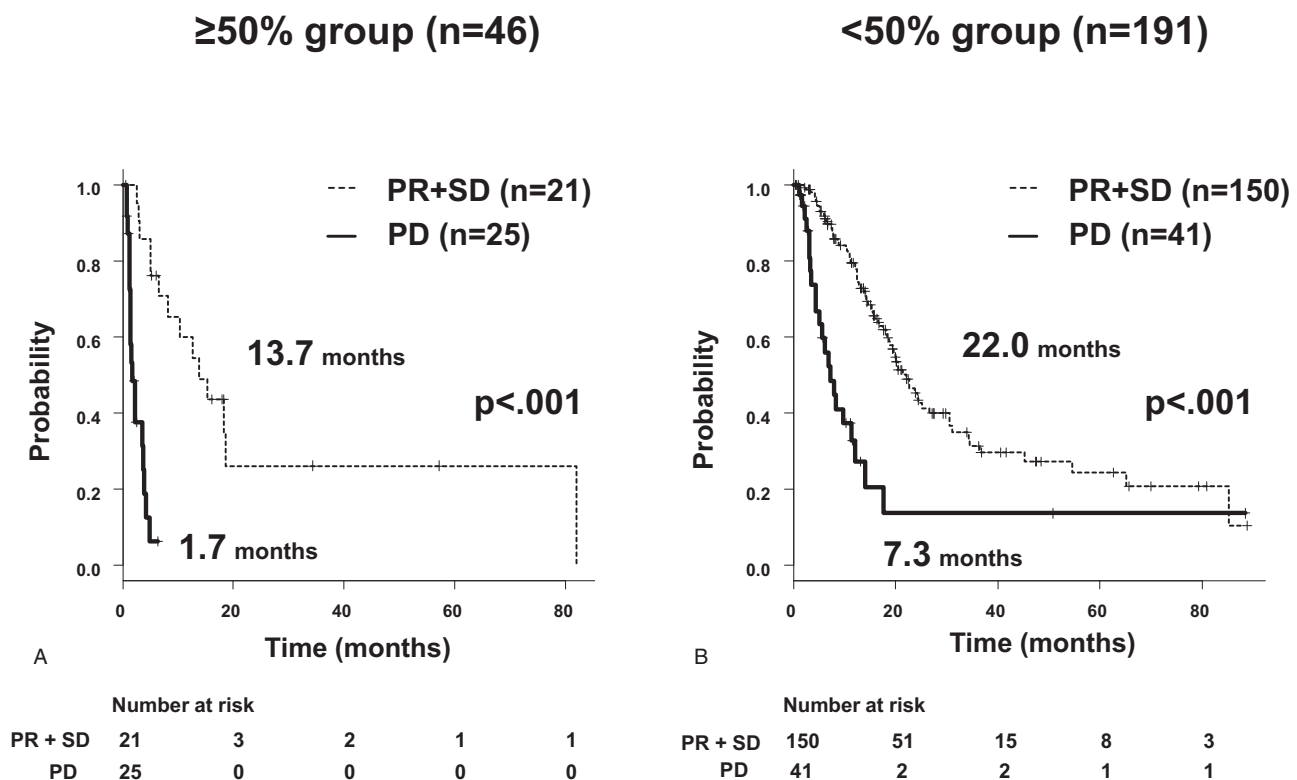| PR + SD	150	51	15	8	3
PD	41	2	2	1	1

Figure 2. Overall survival in patients with PR + SD and PD in the ≥50% group (a) and <50% group (b). PD = progressive disease, PR = partial response, SD = stable disease.
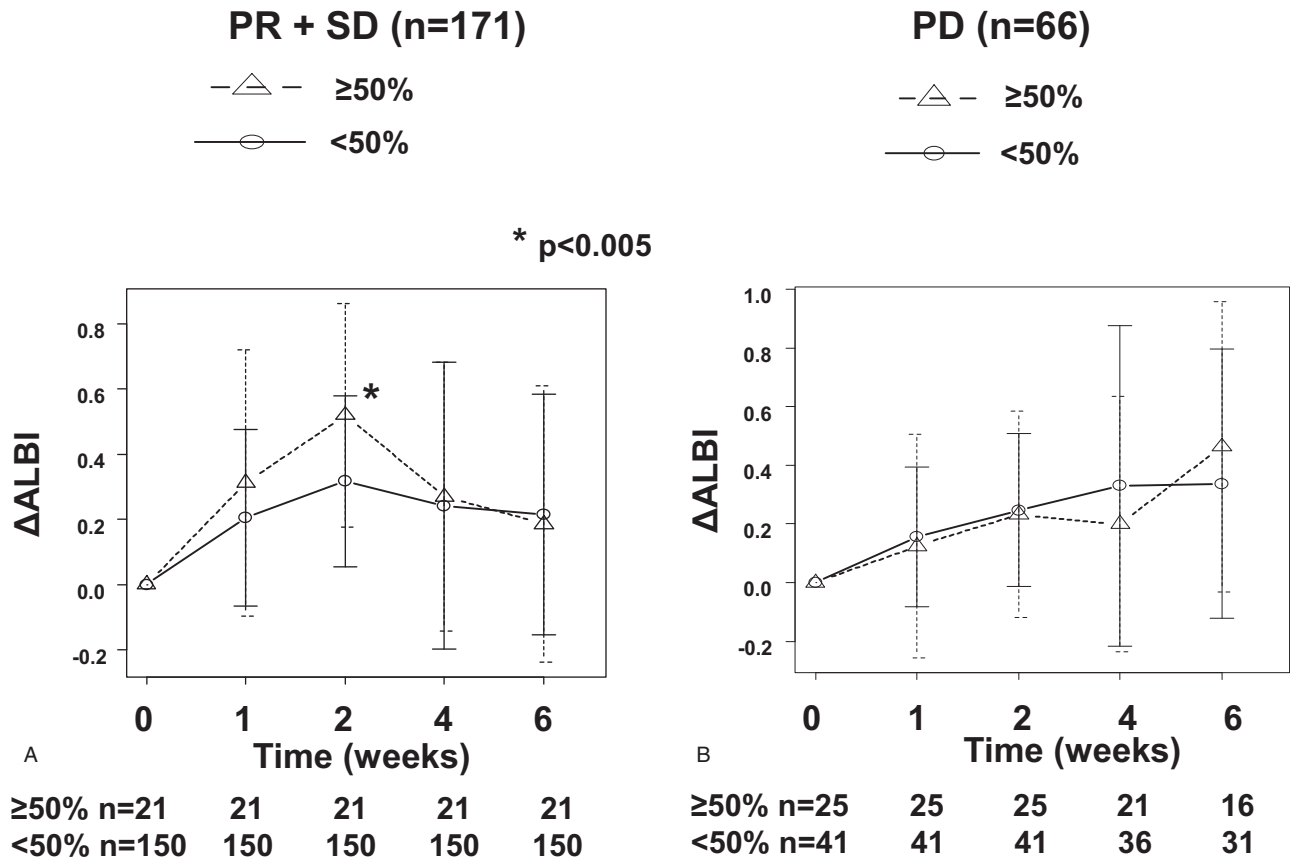
Figure 3. Changes in ΔALBI within 6 wk in the ≥50% and <50% groups by antitumor response. Data represent ± standard error. (a) Patients with PR + SD. (b) Patients with PD. *P < .005 (≥50% vs <50%). ALBI = albumin–bilirubin, PD = progressive disease, PR = partial response, SD = stable disease.

3.4. Changes in ΔALBI in patients with PR + SD and PD at 6 weeks

Figure 3 shows changes in ΔALBI for patients in the ≥50% and <50% groups by antitumor response. Focusing on patients with PR + SD at 6 weeks, ALBI score at 2 weeks was significantly worse in the ≥50% group than in the <50% group. These significant differences between groups had again disappeared at 4 and 6 weeks. Focusing on patients with PD at 6 weeks, ALBI score deteriorated over time in both groups, and no difference between groups was seen in the degree of deterioration in ALBI score within 6 weeks. Portal vein invasion did not significantly change ΔALBI at 2 weeks in either ≥50% or <50% group (Supplementary Table 3, http://links.lww.com/MD/G337). Changes in AST and ALT were also shown in Supplementary Figure 2, http://links.lww.com/MD/G332 and Figure 3, http://links.lww.com/MD/G333.

3.5. Changes in ΔCRP in patients with PR + SD and PD at 6 weeks

Figure 4 shows the transition of ΔCRP within 6 weeks by antitumor response. Focusing on 6-week PR + SD patients, a significant increase in CRP levels at 1 and 2 weeks was evident in the >50% group compared to the <50% group. These significant differences between groups had again disappeared at 4 and 6 weeks. Focusing on patients with PD at 6 weeks, no difference in ΔCRP was seen between groups within 4 weeks, and CRP at 6

weeks was markedly elevated in the ≥50% group compared to the <50% group. Furthermore, in the ≥50% group, patients who obtained PR + SD at 6 weeks had significantly greater ΔCRP at 2 weeks than those with PD (Supplementary Table 4, http://links.lww.com/MD/G338). In the ≥50% group, there was a strong correlation between ΔCRP and ΔALBI at 2 weeks (Spearman's rank correlation coefficient [rs] = 0.686, $P < .001$; Supplementary Figure 4, http://links.lww.com/MD/G334). On the other hand, in the <50% group, the correlation between ΔCRP and ΔALBI at 2 weeks was weak (rs = 0.213, $P = .003$; Supplementary Figure 4, http://links.lww.com/MD/G334).

3.6. Safety

Table 3 shows the frequency of AEs within 6 weeks after starting treatment. Fever of grade 3 or 4 was more common in the ≥50% group (17.1%) than in the <50% group (5.1%, $P = .016$). Median duration of MTA treatment was significantly shorter in the ≥50% group (2.9 months) than in the <50% group (7.7 months, $P < .001$). In the ≥50% group, 14 patients were discontinued within 6 weeks, due to rapid tumor progression in 8 cases, and due to AEs in 6 patients (tumor ruptures, n = 2; pancreatitis, jaundice, loss of appetite, and gastrointestinal bleeding, n = 1 each). In the <50% group, 19 patients were discontinued within 6 weeks. Discontinuation was due to rapid tumor progression in 7 cases, other disease in 1 case, and AEs in 12 cases (rush symptoms, n = 3; liver dysfunction, n = 2;
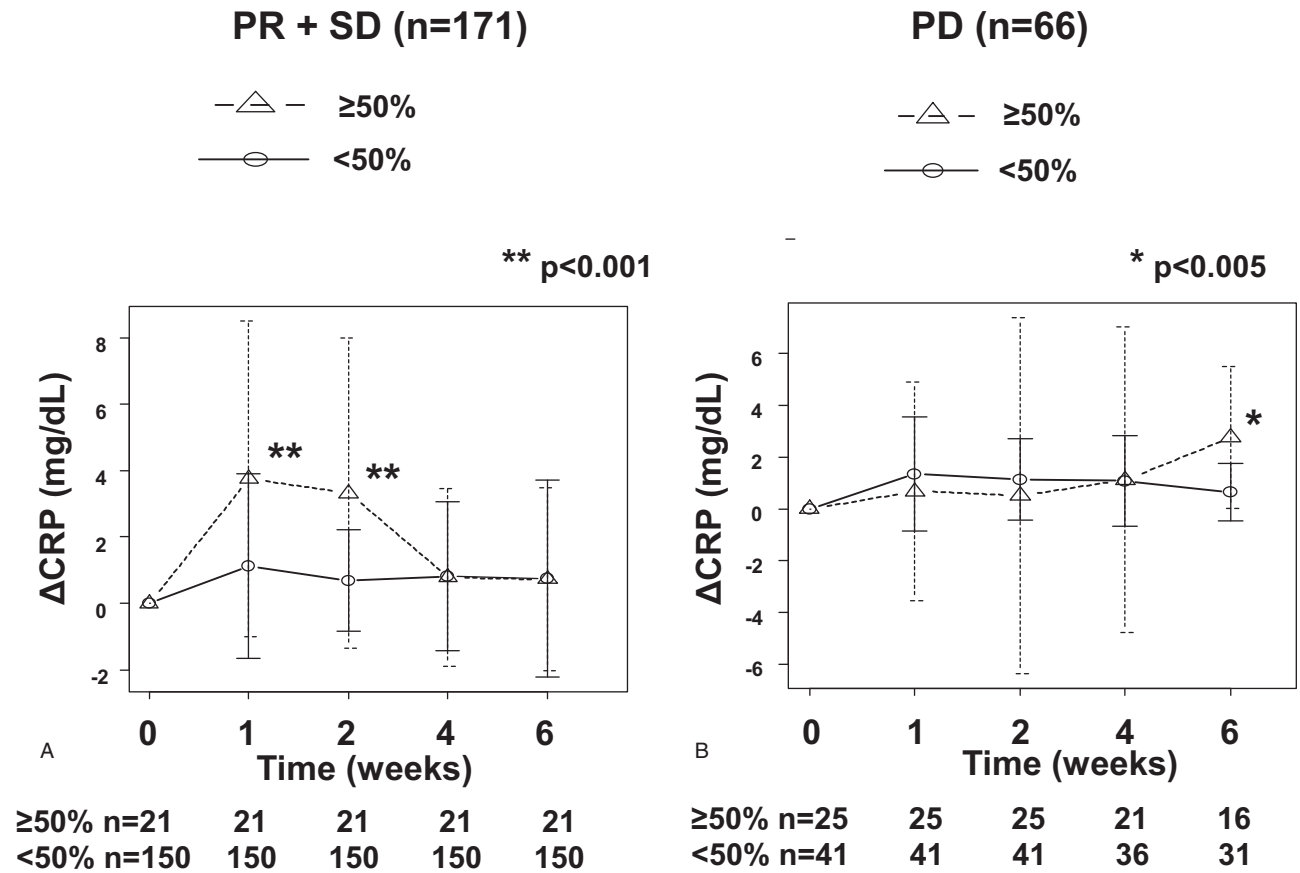
Figure 4. Changes in ΔCRP level within 6 wk in the ≥50% and <50% groups by antitumor response. Data represent ± standard error. (a) Patients with PR + SD. (b) Patients with PD. *P < .005, **P < .001 (≥50% vs <50%). CRP = C-reactive protein, PD = progressive disease, PR = partial response, SD = stable disease.

encephalopathy, n = 2; cerebral hemorrhage, hypertension, diarrhea, loss of appetite, n = 1 each). Decreased appetite of any grade with sorafenib treatment was more common in the ≥50% group (61.1%) than in the <50% group (39.5%, P = .025) (Supplementary Table 5, http://links.lww.com/MD/G339). With lenvatinib treatment, fever was significantly more common in the ≥50% group at any grade (44.4% vs 2.7%, P = .020) and at grades 3 and 4 (22.2% vs 0.0%, P = .035; Supplementary Table 6, http://links.lww.com/MD/G340).

4. Discussion

The present study investigated the outcomes of sorafenib or lenvatinib therapies for unresectable advanced HCC with ≥50% liver occupation, focusing on PR + SD at 6 weeks. Patients with PR + SD at 6 weeks achieved significantly longer OS than those with PD in both the ≥50% group and the <50% group.

In the present study, among patients with 6-week PR + SD, a greater deterioration in ALBI score was observed in the ≥50% group than in the <50% group at 2 weeks after starting treatment. With subsequent adequate management, ALBI score in the ≥50% group improved to the same level as in the <50% group at 4 and 6 weeks. This suggests that more careful dose adjustment is needed early in the course of MTA treatment for patients with ≥50% liver occupation. Although achieving a good antitumor response with MTA treatment in patients with ≥50% liver occupation may contribute to a good prognosis, clinicians should carefully monitor for significant deterioration in hepatic reserve early in the course of treatment and manage the disease appropriately.

Table 3

Adverse events occurring within 6 wk from starting molecularly targeted agents in the ≥50% and <50% groups.

	Any grade			Grade 3 or 4		
	≥50%	<50%	P value	≥50%	<50%	P value
Hand-foot syndrome	22/46 (47.8%)	114/191 (59.7%)	.184	4/46 (8.7%)	35/191 (21.7%)	.127
Diarrhea	13/46 (28.3%)	53/191 (27.7%)	>.99	0/46 (0.0%)	7/191 (3.7%)	.351
Hypertension	16/46 (34.8%)	86/191 (32.6%)	.247	0/46 (0.0%)	10/191 (5.2%)	.216
Decreased appetite	29/46 (63.0%)	90/191 (47.1%)	.070	5/46 (10.9%)	9/191 (4.7%)	.156
Rash	14/46 (30.4%)	62/191 (30.4%)	.862	5/46 (10.9%)	12/191 (6,3%)	.336
Fever	16/41 (39.0%)	51/175 (29.1%)	.261	7/41 (17.1%)	9/175 (5.1%)	.016

Portal vein invasion is known to be one of the factors contributing deterioration in liver function during MTA treatment.[20] However, in this study, the effect of portal vein invasion on liver function was limited at 2 weeks after starting MTA. In addition, our data suggest that in HCC patients with ≥50% liver occupation, an elevated inflammatory response may strongly influence the deterioration of liver function in the early post-dose period.

CRP levels are thought to be associated with tumor burden, as are AST levels, ALT levels, platelet counts, and white blood cell counts.[21–24] Generally, high CRP levels in HCC patients are considered a poor prognostic factor, especially in the presence of large tumors.[24] In fact, these values were significantly higher in the ≥50% group in this study. On the other hand, Zhang et al demonstrated that natural killer cell-mediated innate immunity is necessary for the tumor growth-inhibiting effects of lenvatinib.[25] Sorafenib has also been associated with good antitumor effect with inflammatory reactions such as fever in the early stages of treatment.[26] In patients with HCC who obtain good antitumor response by MTA treatment, the immune response to the tumor might cause strong inflammatory responses and elevated CRP levels. The present study showed that elevated CRP at 2 weeks after starting MTA was associated with a favorable antitumor in the ≥50% group. We also showed that in patients with PR + SD, CRP levels were increased significantly in the ≥50% group than in the <50% group at 1 and 2 weeks. Such strong inflammatory responses might thus have led to decreased hepatic functional reserve at 2 weeks in patients with good antitumor response in the ≥50% group. If CRP is elevated in patients with a large HCC tumor burden early in MTA treatment, a good antitumor response may be achieved, but significant hepatic reserve loss may occur. The clinician must carefully determine how treatment should be continued.

In the present study, general condition and hepatic functional reserve at baseline were significantly worse in the ≥50% group than in the <50% group. In actual clinical practice, MTA treatment for highly advanced HCC may often be administered even for patients with relatively poor general condition and hepatic functional reserve, since no other effective therapeutic options are available. However, poor general condition and low liver function are factors well-known to be associated with poor prognosis following systemic therapy for patients with HCC.[15,27] In fact, limited to patients with PR + SD at 6 weeks, no significant differences in PS, Child-Pugh score, or ALBI score were apparent before starting treatment. Among patients with ≥50% liver occupation, baseline general condition and hepatic functional reserve might be more important factors for safe continuation of MTA treatment, because of the markedly elevated inflammatory response and deteriorated liver function in the early stage of MTA initiation.

Regarding AEs, fever on lenvatinib treatment, and decreased appetite on sorafenib treatment were significantly more frequent in the ≥50% group in the ≥50% group. Median duration of treatment was significantly shorter in the ≥50% group, and a total of 32.6% of patients discontinued treatment within 6 weeks. Recently, it has been reported that lenvatinib often causes hemorrhage in large HCC.[8] Therefore, careful attention should be given to the use of MTA for patients with huge HCC.

Several limitations to the present study need to be considered when interpreting the results. First, we did not compare outcomes between sorafenib and lenvatinib, because we examined early changes in inflammatory response and reserve and prognosis among patients with an antitumor response of PD or better at 6 weeks, regardless of drug type. Although the drugs did not differ significantly between the ≥50% group and the <50% group at pre-treatment baseline or in patients with 6-week PR + SD, the possibility of unintended selection bias cannot be ruled out. Second, CRP can be altered by a variety of factors other than tumors, such as infections, and the present study may not have been able to completely exclude these factors. However, it is very important for clinicians to know that CRP levels, which are commonly used in clinical practice, may elevate in relation to favorable antitumor response in the MTA treatment for patients with high intrahepatic tumor burden. Third, this was a retrospective, nonrandomized study with a small sample size. Confirmation of our findings will require additional studies on a larger number of patients in an independent cohort.

In conclusion, using MTA might be worthwhile in patients with ≥50% liver occupation because the prognosis was significantly prolonged in patients with PR + SD at 6 weeks. However, because of the possibility of transient significant elevation of CRP and worsening of ALBI early after the start of treatment in patients with a good antitumor response, clinicians should monitor the patient closely and manage the disease appropriately.

Author contributions

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References

[1] Manghisi G, Elba S, Mossa A, et al. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 1998;28:751–5.
[2] Miyayama S, Kikuchi Y, Yoshida M, et al. Outcomes of conventional transarterial chemoembolization for hepatocellular carcinoma ≥10 cm. Hepatol Res 2019;49:787–98.
[3] Tsai W-L, Lai K-H, Liang H-L, et al. Hepatic arterial infusion chemotherapy for patients with huge unresectable hepatocellular carcinoma. PLoS One 2014;9:e92784.
[4] Murakami E, Aikata H, Miyaki D, et al. Hepatic arterial infusion chemotherapy using 5-fluorouracil and systemic interferon-α for advanced hepatocellular carcinoma in combination with or without three-dimensional conformal radiotherapy to venous tumor thrombosis in hepatic vein or inferior vena. Hepatol Res 2012;42:442–53.
[5] Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
[6] Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163–73.
[7] Maruta S, Ogasawara S, Ooka Y, et al. Potential of lenvatinib for an expanded indication from the REFLECT trial in patients with advanced hepatocellular carcinoma. Liver Cancer 2020;9:382.

[8] Uchida-Kobayashi S, Kageyama K, Yamamoto A, et al. Lenvatinib-induced tumor-related hemorrhages in patients with large hepatocellular carcinomas. Oncology 2020;99:186–91.

[9] Ogasawara S, Kanai F, Ooka Y, et al. Initial response to sorafenib by using enhancement criteria in patients with hepatocellular carcinoma. Hepatol Int 2013;7:703–13.

[10] Hiraoka A, Kumada T, Atsukawa M, et al. Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions—multicenter analysis. Cancer Med 2019;8:3719–28.

[11] Kuzuya T, Ishigami M, Ishizu Y, et al. Early clinical response after 2 weeks of sorafenib therapy predicts outcomes and anti-tumor response in patients with advanced hepatocellular carcinoma. PLoS One 2015;10: e0138776.

[12] Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–905.

[13] Johnson PJ, Berhane S, Kagebayashi C, et al. A nssessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach – the albi grade. J Clin Oncol 2015;33:550–8.

[14] Shingina A, Hashim AM, Haque M, et al. In a "real-world", clinic-based community setting, sorafenib dose of 400 mg/day is as effective as standard dose of 800 mg/day in patients with advanced hepatocellular carcimona, with better tolerance and similar survival. Can J Gastroenterol 2013;27:393–6.

[15] Kudo M, Ikeda M, Takayama T, et al. Safety and efficacy of sorafenib in Japanese patients with hepatocellular carcinoma in clinical practice: a subgroup analysis of GIDEON. J Gastroenterol 2016;51:1150–60.

[16] Hiraoka A, Kumada T, Kariyama K, et al. Therapeutic potential of lenvatinib for unresectable hepatocellular carcinoma in clinical practice: multicenter analysis. Hepatol Res 2019;49:111–7.

[17] Kuzuya T, Ishigami M, Ito T, et al. Favorable radiological antitumor response at 2 weeks after starting lenvatinib for patients with advanced hepatocellular carcinoma. Hepatol Res 2020;50:374–81.

[18] Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.

[19] Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant 2013;48:452–8.

[20] Kaneko S, Tsuchiya K, Yasui Y, et al. Strategy for advanced hepatocellular carcinoma based on liver function and portal vein tumor thrombosis. Hepatol Res 2020;50:1375–85. hepr.13567.

[21] Akkiz H, Carr BI, Kuran S, et al. Macroscopic portal vein thrombosis in HCC patients. Can J Gastroenterol Hepatol 2018;2018:3120185.

[22] Carr BI, Guerra V. Hepatocellular carcinoma size: platelets γ-glutamyl transpeptidase, and alkaline phosphatase. Oncol 2013;85:153–9.

[23] Ni XC, Yi Y, Fu YP, et al. Prognostic value of the modified glasgow prognostic score in patients undergoing radical surgery for hepatocellular carcinoma. Med (United States) 2015;94:e1486.

[24] Jun CH, Ki HS, Lee KH, et al. Impact of serum C-reactive protein level on the prognosis of patients with hepatocellular carcinoma undergoing TACE. Clin Mol Hepatol 2013;19:70–7.

[25] Zhang Q, Liu H, Wang H, et al. Lenvatinib promotes antitumor immunity by enhancing the tumor infiltration and activation of NK cells. Am J Cancer Res 2019;9:1382–95.

[26] Kuzuya T, Ishigami M, Ishizu Y, et al. Fever within 2 weeks of sorafenib therapy predicts favorable treatment efficacy in patients with advanced hepatocellular carcinoma. Oncol 2016;91:261–6.

[27] Rovesti G, Orsi G, Kalliopi A, et al. Impact of baseline characteristics on the overall survival of HCC patients treated with sorafenib: ten years of experience. Gastrointest Tumors 2019;6:92–107.