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Evaluation of Atezolizumab Plus Bevacizumab *Versus* Modified Lenvatinib Therapy in Child-Pugh A Unresectable Hepatocellular Carcinoma

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Abstract. *Background/Aim: Atezolizumab/bevacizumab (Atez/BV) and lenvatinib (LEN) are the recommended first-line treatments for patients with unresectable hepatocellular carcinoma (HCC). Previous reports have suggested that the tolerability and therapeutic efficacy of LEN could be enhanced by modifying its administration method. Therefore, this study compared the efficacy and safety of Atez/BV, the standard LEN therapy (standard LEN), and modified LEN therapy (modified LEN). Patients and Methods: The overall survival (OS) and the rate of discontinuation due to adverse events (AEs) were compared between groups treated with Atez/BV (n=36), standard LEN (n=30), and modified LEN (n=11). Results: Discontinuation due to AEs was required in 22.2%, 23.3%, and 9.1% of patients in the Atez/BV, standard LEN, and modified LEN groups (p=0.485). The median OS for the Atez/BV, standard LEN, and modified LEN groups was 523 [95% confidence interval (CI)=163-818], 382 (95%CI=330-547), and 604 (95% CI=257-656) days, respectively (log-rank test, p=0.949). Conclusion: Atez/BV and the standard and modified LEN regimens showed comparable efficacy and safety.*

The combination of atezolizumab (Atez), a humanized immunoglobulin G1 (IgG1) monoclonal antibody targeting programmed death-ligand 1 (PD-L1), and bevacizumab (BV), a monoclonal antibody that targets vascular endothelial growth factor (VEGF) and inhibits angiogenesis and tumor growth, is the recommended first-line treatment for patients with unresectable hepatocellular carcinoma (HCC) and Child-Pugh A (CP-A) liver function (1-4). Lenvatinib (LEN), another drug used for treating unresectable HCC, is an oral multikinase inhibitor that selectively inhibits receptor tyrosine kinases (5).

The Atez/BV combination is recommended over LEN because the latter could not prolong survival compared to sorafenib and has only shown non-inferiority (6). However, sorafenib and lenvatinib are recommended for cases in which treatment with Atez/BV is not appropriate due to comorbidities such as autoimmune diseases. Furthermore, given the convenience of LEN as an oral drug, it has become a treatment option in clinical practice depending on the patient's wishes.

Regarding the efficacy of Atez/BV and LEN, which are the first-line treatments for unresectable HCC, there are reports (7-9) that the progression-free survival (PFS) and overall survival (OS) were similar with both treatments. However, it has also been reported that the Atez/BV combination was more effective than LEN (10-12). Thus, the current evidence is inconsistent. Some studies have investigated whether LEN tolerability and efficacy can be enhanced by modifying the dosing regimen, such as 5 days of drug administration with 2-day intervals (weekends-off) and alternate-day administration (13). In particular, the weekends-off method allowed for a longer treatment duration than the alternate-day or the standard LEN regimens (14). Therefore, LEN with a better administration method may be superior to Atez/BV in terms of treatment duration and OS. Clarifying the efficacy and safety of the Atez/BV combination and LEN therapy with a modified administration method for first-line treatment should help in treatment selection and adverse event management.

In this study, we compared the efficacy and safety of Atez/BV, standard LEN therapy, and modified LEN therapy for the first-line treatment of unresectable HCC.

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Key Words: Atezolizumab, bevacizumab, lenvatinib, first-line treatment, overall survival, unresectable hepatocellular carcinoma.

Patients and Methods

Patients and evaluations. The data of 77 patients treated with Atez/BV or LEN as first-line treatment for HCC at Ogaki Municipal Hospital (Ogaki, Japan) between January 2018 and September 2023 were retrospectively evaluated. LEN-administered patients were divided into those who completed treatment with the standard administration method (standard LEN) and those who changed from the standard administration method to a modified method during treatment [modified LEN (weekends-off/alternate-day)]. We analyzed the patient characteristics, treatment duration, overall survival (OS), adverse events (AEs), and LEN-related reasons for discontinuation over the treatment duration. Data were analyzed using electronic charts and pharmacy service records. AEs were evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0 (15), and AEs with the highest grades during chemotherapy were reported. Personal information in the aggregated data was protected. This study was approved by the Institutional Review Board of Ogaki Municipal Hospital (Ogaki, Japan; approval number: 20231026-14). The need for informed consent was waived owing to the retrospective nature of the study.

Treatment protocol. Atez was administered intravenously at 1,200 mg over 60 min on the first day. If the first dose was well tolerated, the duration of the second infusion was shortened to 30 min. BV was administered intravenously at 15 mg/kg over 90 min on the first day. If no problems were encountered, the durations of the second and third infusions were shortened to 60 min and 30 min, respectively. This procedure was repeated every 21 days.

The dose of LEN was based on body weight: the initial dose was 12 mg/day for those weighing ≥60 kg and 8 mg/day for those weighing <60 kg. During the 28-day cycles, dose adjustment, including reduction to 8 or 4 mg/day, 4 mg every other day, or interruption, was allowed for LEN based on AEs (6, 16). In patients who experienced unacceptable drug-related AEs, the LEN dose was reduced or treatment was interrupted, according to manufacturer instructions. Dose reduction or temporary interruption of LEN was maintained until the AE severity dropped to grade 1 or 2. In cases where dose reduction was maintained, the reduced doses administered were 20, 14, 10, 8, or 4 mg once daily.

Statistical analysis. Between-group comparisons were performed using the F-test. Kruskal–Wallis tests or chi-square tests of independence (Fisher's exact probability tests) were used to compare patient characteristics, AEs, and reasons for discontinuation. Kaplan–Meier and log-rank tests were used to compare treatment durations and OS. Differences were considered statistically significant at $p<0.05$. All analyses were performed using the EZR software (version 1.30; Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for the R software (The R Foundation for Statistical Computing, Vienna, Austria) (17).

Results

Patient characteristics. The Atez/BV, standard LEN, and modified LEN groups (weekends-off/alternate-day) included 36, 30, and 11 (2/9) patients, respectively. Patient characteristics are summarized in Table I. Regarding patient backgrounds, a significant difference was noted between the three groups in terms of having a history of transcatheter arterial chemoembolization.

Reasons for discontinuation. The reasons for discontinuation in the Atez/BV, standard LEN, and modified LEN groups are summarized in Table II. The rate of discontinuation due to AEs did not differ between the groups ($p=0.485$). In addition, the three groups showed no significant differences in the rates of progressive disease, AEs, performance status deterioration, or condition deterioration. In the Atez/BV group, treatment was discontinued in eight patients due to drug eruption, hand-foot syndrome (HFS), anemia, diarrhea, fatigue, renal impairment/hyperkalemia, liver impairment, and pancytopenia. Only one patient required treatment discontinuation in the modified LEN group due to worsening renal function. However, in the standard LEN group, seven patients required discontinuation because of abdominal pain, anorexia/inability to move or stand, diarrhea/vomiting/abdominal bloating, proteinuria, anorexia, poor oral intake, and nausea/hoarseness. Other reasons for discontinuation were as follows: ruptured hepatocellular carcinoma, surgery, and esophageal varices in the Atez/BV group; suspected pneumatosis intestinalis in the modified LEN group; and cerebral hemorrhage and accidental ingestion in the standard LEN group.

Transition to second-line treatment occurred in 13/29 (44.8%), 12/29 (41.4%), and 7/11 (63.6%) patients in the Atez/BV, standard LEN, and modified LEN groups, respectively.

Frequency of AEs. The AEs in the Atez/BV- and LEN administered groups are summarized in Table III. Blood bilirubin levels increased more frequently with LEN (18 patients) than with Atez/BV (2 patients) ($p<0.001$). HFS was also more common with LEN (10 patients) than with Atez/BV (2 patients) ($p=0.001$). Moreover, the incidence of proteinuria was higher with LEN (16 patients) than with Atez/BV (six patients) ($p=0.030$). However, skin disorders occurred more frequently with Atez/BV (one patient) than with LEN (10 patients) ($p=0.002$). Increased creatinine levels were also more common with Atez/BV (12 patients) than with LEN (one patient) ($p<0.001$). Similarly, increased creatine kinase (CPK) levels were more frequently observed with Atez/BV (seven patients) than with LEN (zero patients) ($p=0.006$). Grade 3 or higher AEs occurred in 10/36 patients (30.5%) treated with Atez/BV and 19/41 patients (46.3%) treated with LEN ($p=0.093$).

Efficacy of Atez/BV and LEN. The Kaplan–Meier survival curves for the treatment duration in patients administered Atez/BV or LEN are shown in Figure 1. The median treatment duration for the Atez/BV, standard LEN, and modified LEN groups was 128.5 [95% confidence interval (CI)=68-231],

Table I. *Patient characteristics*.

Characteristic	Atez/BV	Standard LEN	Modified LEN	*p*-Value
Patients, n	36	30	11	
Age, years				
Median (range)	73 (57-85)	77 (58-86)	77 (67-88)	0.508[a]
Sex, n				
Male/female	22/14	26/4	9/2	0.051[b]
Height, cm				
Median (range)	163 (145-169)	161 (127-171)	165 (158-171)	0.239[a]
Weight, kg				
Median (range)	60.5 (42-92)	59 (40-98)	69 (53-88)	0.138[a]
Body surface area, kg/m^2				
Median (range)	1.67 (1.38-2.01)	1.61 (1.17-2.01)	1.71 (1.53-1.99)	0.051[a]
Creatinine clearance, ml/min				
Median (range)	64.8 (28.4-132.4)	64.2 (16.6-163.8)	61.9 (37.7-93.3)	0.948[a]
Cause of hepatocellular carcinoma, n				
Hepatitis B virus	12	4	2	0.146[b]
Hepatitis C virus	6	12	5	0.057[b]
Non-B non-C	18	14	4	0.729[b]
Performance status, n				
0	29	20	8	0.438[b]
1	7	8	3	0.746[b]
2	0	2	0	0.200[b]
Past history of transcatheter arterial chemoembolization, n				
Yes	19	24	10	0.014[b]

[a]Kruskal-Wallis test. [b]chi-square tests of independence (Fisher's exact probability tests). Atez/BV: Atezolizumab/bevacizumab; LEN: lenvatinib.

Table II. *Reasons for discontinuation of treatment*.

Events	Atez/BV n=36	Standard LEN n=30	Modified LEN n=11	*p*-Value
Progressive disease	10	13	8	0.095[a]
Adverse events	8	7	1	0.485[a]
Deterioration in performance status	3	4	0	0.435[a]
Deterioration of condition	4	2	1	0.679[a]
Others	4	2	1	0.679[a]
Ongoing	7	1	0	

[a]Chi-square tests of independence (Fisher's exact probability tests). Atez/BV: Atezolizumab/bevacizumab; LEN: lenvatinib.

113.0 (95%CI=67-189), and 343.0 (95%CI=120-560) days, respectively (log-rank test, p=0.257).

The Kaplan–Meier survival curves for the OS of patients administered Atez/BV or LEN are shown in Figure 2. The median OS for the Atez/BV, standard LEN, and modified LEN groups was 523 (95%CI=163-818), 382 (95%CI=330-547), and 604 (95%CI=257-656) days, respectively (log-rank test, p=0.949).

Discussion

This study compared the efficacy and safety of Atez/BV and LEN in three groups that were administered either Atez/BV, standard LEN therapy, or a modified LEN regimen. The survival curves of the Atez/BV and LEN groups in this study were not significantly different and tended to overlap. Some studies have investigated the effect of modifying the administration method for LEN on its therapeutic effects (13, 14). Iwamoto *et al*. reported that the treatment period and duration of survival for LEN were significantly prolonged with the weekends-off administration method compared to those with the standard administration method (13). Kimura *et al*. also showed that the weekends-off method allowed for a longer treatment duration than the alternate-day or standard LEN methods (14). Therefore, it was expected that using LEN with a better administration method would result in longer

Table III. *Adverse events*.

Events	Atez/BV					LEN (Modified LEN and standard LEN)					*p*-Value
	Grade					Grade					
	1	2	3	4	All grades (%)	1	2	3	4	All grades (%)	
Leucopenia	10	4	0	0	14 (38.9)	5	7	1	0	13 (31.7)	0.510[a]
Neutropenia	7	4	1	0	12 (33.3)	2	5	3	0	10 (24.4)	0.386[a]
Aspartate Aminotransferase/alanine aminotransferase increased	20	2	1	0	23 (63.9)	19	1	0	0	20 (48.8)	0.182[a]
Blood bilirubin increased	1	1	0	0	2 (5.6)	9	7	2	0	18 (43.9)	<0.001[a]
Anemia	12	4	1	0	17 (47.2)	15	3	2	0	20 (48.8)	0.891[a]
Platelet count decreased	11	7		0	18 (50.0)	17	10	1	0	28 (68.3)	0.103[a]
Hypertension	7	0	0	0	7 (19.4)	9	4	2	0	15 (36.6)	0.097[a]
Hand-foot-syndrome	0	1	1	0	2 (5.6)	6	4	0	0	10 (24.4)	0.001[a]
Anorexia	1	4	2	0	7 (19.4)	11	3	1	0	15 (36.6)	0.097[a]
Proteinuria	2	4	0	–	6 (16.7)	1	10	5	0	16 (39.0)	0.030[a]
Fatigue	6	1	1	0	8 (22.2)	11	2	1	0	14 (34.1)	0.248[a]
Hoarseness	0	0	0	0	0 (0)	4	0	0	0	4 (9.8)	0.054[a]
Edema limbs	3	0	0	–	3 (8.3)	8	0	0	0	8 (19.5)	0.162[a]
Nausea	1	1	0	0	2 (5.6)	3	2	0	0	5 (12.2)	0.312[a]
Vomiting	0	0	0	0	0 (0)	2	0	0	0	2 (4.9)	0.179[a]
Hyperkalemia	1	0	0	0	1 (2.8)	1	0	0	0	1 (2.4)	0.926[a]
Diarrhea	4	0	1	0	5 (13.9)	5	0	1	0	6 (14.6)	0.926[a]
Dizziness	0	0	0	–	0 (0)	1	0	0	0	1 (2.4)	0.346[a]
Hypothyroidism	3	1	0	0	4 (11.1)	2	3	0	0	5 (12.2)	0.883[a]
Rash	7	3	0	0	10 (27.8)	1	0	0	0	1 (2.4)	0.002[a]
Pruritus	3	0	0	–	3 (8.3)	0	0	0	0	0 (0)	0.059[a]
Epistaxis	0	0	0	0	0 (0)	1	0	0	0	1 (2.4)	0.346[a]
Stomatitis	1	0	0	0	1 (2.8)	2	0	0	0	2 (4.9)	0.634[a]
Dizziness	1	0	0	0	1 (2.8)	1	0	0	0	1 (2.4)	0.926[a]
Creatinine increased	11	0	1	0	12 (33.3)	0	1	0	0	1 (2.4)	<0.001[a]
Constipation	2	0	0	0	2 (5.6)	0	0	0	0	0 (0)	0.126[a]
Abdominal pain	0	0	0	0	0 (0)	2	0	0	0	2 (4.9)	0.179[a]
Dysgeusia	1	0	0	0	1 (2.8)	0	0	0	0	0 (0)	0.282[a]
Arthritis	1	0	0	0	1 (2.8)	0	0	0	0	0 (0)	0.282[a]
CPK increased	3	2	1	1	7 (19.4)	0	0	0	0	0 (0)	0.006[a]
Rhabdomyolysis	0	2	0	0	1 (2.8)	0	0	0	0	0 (0)	0.282[a]
Others	3	0	0	0	3 (8.3)	4	0	0	0	4 (9.8)	0.828[a]

[a]Chi-square tests of independence (Fisher's exact probability tests). Atez/BV: Atezolizumab/bevacizumab; LEN: lenvatinib; CPK: creatine kinase.

treatment duration and OS than those with Atez/BV. However, in this study, the treatment duration and OS with the modified LEN administration method were comparable to those with the standard LEN administration method and Atez/BV. This may be because only two of the 11 patients in the modified LEN group received the weekends-off regimen. In the report by Kimura *et al*., the treatment duration with the weekends-off method was longer than that with the standard LEN method, whereas the duration with the alternate-day method was equivalent to that with the standard LEN method (14).

In a recently published meta-analysis, immune checkpoint inhibitors showed limited efficacy in patients with non-alcoholic fatty liver disease (NAFLD)-related HCC. This is likely because the NAFLD-associated aberrant T-cell activation causes tissue damage and leads to impaired immune surveillance (18). It has been reported that Atez/BV is less effective in HCC without a viral etiology than in HCC with a viral etiology and that Atez/BV is particularly less effective in patients with NAFLD-related HCC (7, 8). Therefore, in patients with NAFLD-related HCC, the weekends-off LEN regimen may be more effective than the standard LEN regimen, which should be investigated in future studies.

Regarding the reasons for treatment discontinuation, Maesaka *et al*. (10) reported that the discontinuation rate due to AEs was higher with LEN than with Atez/BV. In this study, there was no difference in the rate of discontinuation due to AEs between the Atez/BV group and the two LEN

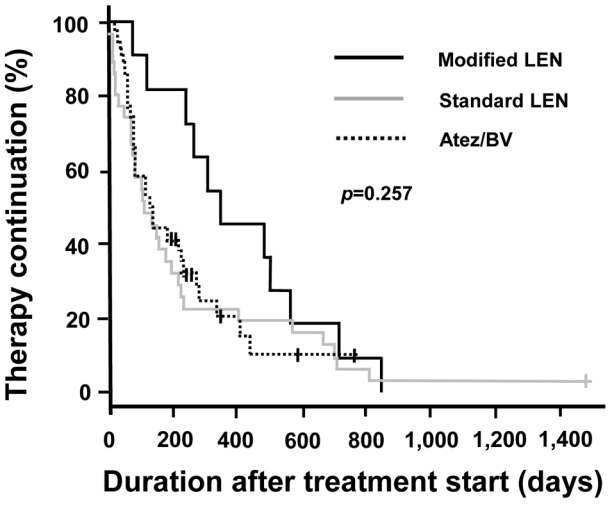

Figure 1. *Kaplan–Meier survival curves of treatment duration following first-line therapy with atezolizumab/bevacizumab and lenvatinib (standard administration method and those who changed from the standard administration method to a modified method in the middle of treatment). No significant difference in survival was observed between the three groups.*

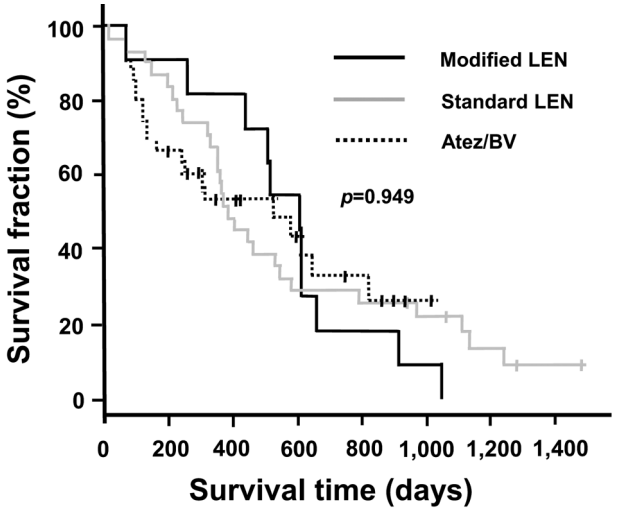

Figure 2. *Kaplan–Meier survival curves of overall survival following first-line therapy with atezolizumab/bevacizumab and lenvatinib (standard administration method and those who changed from the standard administration method to a modified method in the middle of treatment). No significant difference in survival was observed between the three groups.*

groups. This could be because the rate of discontinuation due to AEs was lower in the modified LEN group than in the standard LEN group due to the improved administration method, which made it possible to continue treatment. In this study, discontinuation due to AEs was observed in seven patients in the standard LEN group and one patient in the modified LEN group. Therefore, it can be said that the modified LEN regimen is useful in terms of safety. In the Atez/BV group, eight patients required treatment discontinuation due to various AEs. Thus, the Atez/BV combination requires monitoring not only for immune-related AEs (irAEs) but also for other AEs.

Concerning the frequency of AEs with Atez/B and LEN, HFS was more common with LEN than with Atez/BV, which is consistent with the findings of Hiraoka *et al*. (11) and Niizeki *et al*. (12). In this study, proteinuria was more common with LEN than with Atez/BV, but this difference in incidence was not observed in the studies by Hiraoka *et al*. (11) and Niizeki *et al*. (12). The incidence rate of proteinuria with LEN in this study was 39.0%, which is higher than the 24.6%, 23.6%, and 17.1% observed in previous studies. The cause of this difference in incidence is unknown. Rashes were more common with Atez/BV than with LEN, which agrees with the findings of Niizeki *et al*. (12) and Kim *et al*. (9). On the contrary, in the study by Hiraoka *et al*. (11), the frequency of rash was similar with LEN and Atez/BV. Increased creatinine and CPK levels were also more common with Atez/BV than with LEN, which is consistent with the characteristics of Atez, an immune checkpoint inhibitor that causes irAEs. In addition, two cases of rhabdomyolysis were observed in the Atez/BV group.

The Kaplan–Meier survival curves for treatment duration showed that the treatment duration in the modified LEN group tended to be longer than that in the Atezo/BV group (not shown in the results, p=0.065). Unfortunately, in this study, most results related to LEN were associated with the alternate-day regimen, and there is a possibility that the difference in treatment duration with the weekends-off regimen would be significant, which should be considered in future studies. This is because the weekends-off regimen was associated with a longer treatment duration than the alternate-day and standard regimens (14). Moreover, in this study, we compared Atez/BV and LEN as first-line treatments, but it is hoped that appropriate LEN administration methods for subsequent lines of therapy are considered in future studies, especially given that the usefulness of LEN after Atez/BV treatment has been previously demonstrated (19, 20). It is also necessary for such studies to involve patients with NAFLD-related HCC.

The limitations of this study include the relatively short observation period, limited sample size, and its retrospective, single-center nature. Owing to the small sample size, this study may not have had sufficient statistical power to obtain accurate estimates. In some cases, treatment response (progressive disease, stable disease, and partial response) could not be analyzed because information regarding tumor

size could not be obtained. In addition, LEN was introduced before Atez/Bev. The observation period for the Atez/Bev group was also short, and a longer observation period is required to reach definitive conclusions. Future studies should address these limitations.

Conclusion

Atez/BV, standard LEN therapy, and modified LEN therapy exhibited comparable efficacy and safety as first-line treatments for unresectable HCC. Our findings regarding the efficacy and tolerability of these therapies could aid in treatment selection and the management of AEs. Further studies with larger sample sizes and longer follow-up periods are needed to validate these results.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

MK contributed to the study design, collected and provided data, was the principal author of the article, and is the guarantor of the article and all data. SY, MG, SY, HT, and EU contributed to the clinical study design, reviewed the article, and supervised the article preparation and publication processes. All Authors approved the final version of the manuscript.

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