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First-Line Durvalumab plus Tremelimumab Treatment for Unresectable Hepatocellular Carcinoma in Real-World Clinical Practice

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Keywords
Hepatocellular carcinoma · Immune checkpoint inhibitors · Durvalumab · Tremelimumab · Positron emission tomography

Abstract
Introduction: Durvalumab plus tremelimumab combination therapy (STRIDE regimen) is a new first-line option for unresectable hepatocellular carcinoma (uHCC), but little real-world data are available to determine which patients are most likely to respond. ***Methods:*** This study retrospectively evaluated patients with uHCC who were treated with the STRIDE regimen as the 1st line at our hospital. The primary endpoint of the study was the objective response rate (ORR). We focused on identifying factors associated with cases that had a favorable response. ***Results:*** Twenty-one patients were included. In best response, there were 11 partial response cases, with an ORR of 52.4%. Median progression-free survival was 6.8 months, and overall survival did not reach the median time. A high tumor-to-liver ratio of the maximum value of the standardized uptake value (TLR) on baseline fluorodeoxyglucose positron emission tomography (FDG-PET) was associated with response, while TLRs were significantly higher in poorly differentiated uHCC. ***Conclusion:*** The STRIDE regimen may be beneficial for systemic therapy-naive uHCC patients. High TLR on baseline FDG-PET could be a potentially useful biomarker for response.

Introduction

Recently, the phase III HIMALAYA trial demonstrated the superiority of durvalumab (anti-PD-L1 inhibitor) and tremelimumab (anti-CTLA-4 inhibitor) combination therapy (STRIDE regimen) over sorafenib [1], establishing a new first-line option for unresectable hepatocellular carcinoma (uHCC). Another immune checkpoint inhibitor (ICI) option for uHCC is atezolizumab plus bevacizumab therapy (Atezo/Bev) [2], but the therapeutic benefits of ICI vary greatly from case to

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Table 1. Clinical characteristics of the patients

Variable (n = 21)	
Age, median	73 (37–92)
Sex, female/male	3/18
Platelet, median, $\times 10^4/\mu L$	15.1 (7.3–24.7)
PLR, median	119.7 (31.2–209.2)
NLR, median	1.9 (0.8–6.1)
PT, median, %	83 (71–107)
Albumin, median, g/dL	3.9 (2.8–4.9)
Total bilirubin, median, mg/dL	0.7 (0.4–1.9)
AST, median, IU/L	31 (18–173)
ALT, median, IU/L	28 (9–107)
γGTP, median, IU/L	70 (19–490)
AFP, median, ng/mL	19.9 (1.7–689,460)
DCP, median, mAU/mL	827 (16–148,062)
Child-Pugh score, 5/6	16/5
ALBI grade, G1/G2	10/11
Main tumor size, median, mm	33 (10–130)
Intrahepatic tumor number, 0/1/Multi	4/6/11
T, 0/1/2/3/4	4/0/6/7/4
N, 0/1	16/5
M, 0/1	14/7
MVI, Vp3/Vp4/Vv	4/1/2
TNM staging, 1/2/3/4a/4b	0/4/5/5/7
BCLC staging, A/B/C	3/5/13
Etiology (HBV/HCV/NBNC)	6/6/9

PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, γ-glutamyl transpeptidase; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy pro-thrombin; ALBI, albumin-bilirubin; TNM, tumor, node, metastasis; MVI, macroscopic portal vein invasion; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C.

case. While the STRIDE regimen is expected to produce long-term responses, there are many cases in which response is not achieved. In subgroup analysis of the HIMALAYA trial, treatment effects of the STRIDE regimen versus sorafenib were generally consistent across the clinically relevant subgroups and superior with the STRIDE regimen [1]; however, it is not known in which cases the STRIDE regimen will achieve a favorable response.

In this study, we analyzed the overall therapeutic outcomes of the initial experience with the STRIDE regimen for uHCC. In particular, we focused on identifying factors associated with cases that had a favorable response.

Method

Study Design and Patients

This study retrospectively evaluated 21 patients with uHCC who were treated with the STRIDE regimen as the 1st line at the Hiroshima University Hospital between April 2023 and December 2023. The exclusion criteria were as follows: (i) Child-Pugh liver function class B or C, (ii) age <18 years, (iii) performance status score of 2 or more, and (iv) were not evaluated by Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) [3]. The end of follow-up was March 2024, and the median follow-up period was 8.8 months. The primary endpoint of the study was the objective response rate (ORR). The histological classification for HCC tissues was diagnosed by pathologists based on the 2019 WHO classification [4]. The study protocol was approved by the Hiroshima University Ethical Committee (approval number E2012-0726) in accordance with the Declaration of Helsinki [5]. All patients provided written informed consent.

Treatment Protocol

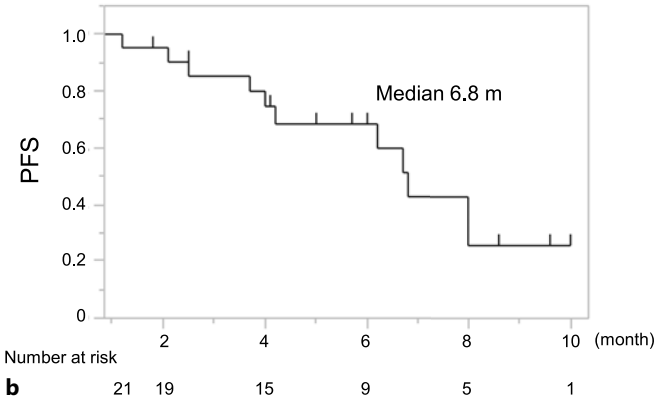
Patients received the STRIDE regimen, consisting of one dose of 300 mg of tremelimumab plus 1,500 mg of durvalumab, followed by 1,500 mg of durvalumab every 4 weeks. Patients received the treatment until the development of unacceptable adverse events or tumor progression.

Imaging Evaluation and Outcome Measures

It has been reported that fluorodeoxyglucose positron emission tomography (FDG-PET) allows the detection of the spread of HCC in patients with advanced HCC [6], so we routinely perform it prior to treatment. The maximum value of the standardized uptake value (SUVmax) on FDG-PET was measured by a radiology specialist for intrahepatic lesions and, if absent, for major metastatic lesions. The tumor-to-liver ratio of the SUVmax (TLR) was defined as follows: SUVmax of the tumor/SUVmax of normal liver tissue. Tumors were assessed by CT or MRI 4 weeks after the initiation of treatment and every 2 months after that. The therapeutic response was evaluated according to the RECIST 1.1 [3] and modified RECIST (mRECIST) guidelines [7]. The ORR was

	RECIST	mRECIST
	n=21 (%)	n=21 (%)
PR	11 (52.4)	12 (57.1)
SD	4 (19.0)	2 (9.5)
PD	6 (28.6)	6 (28.6)
NE	0	1 (4.8)
ORR	11 (52.4)	12 (57.1)
DCR	15 (71.4)	14 (66.7)

a



b

Fig. 1. Overall therapeutic outcomes of the STRIDE regimen. **a** Best response evaluated with RECIST 1.1 and mRECIST is shown. **b** Kaplan-Meier curve estimates of PFS. PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; DCR, disease control rate; PFS, progression-free survival.

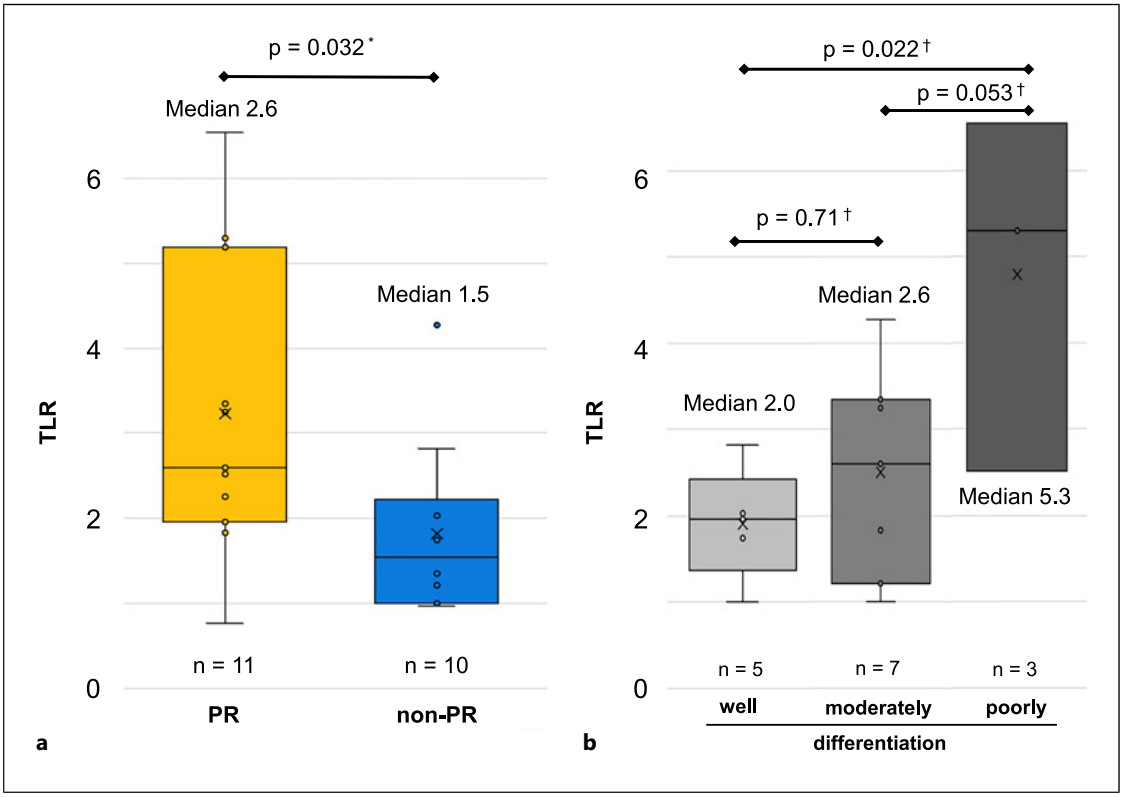


Fig. 2. Association between TLRs and response and tumor differentiation. **a** Association between the TLRs on baseline FDG-PET and response. **b** Association between the TLRs and tumor differentiation. TLR, the tumor-to-liver ratio of the maximum value of the standardized uptake value. *Mann-Whitney U test. †Tukey's honestly significant difference test.

Table 2. Prognostic baseline factors for PR for the STRIDE regimen

Variable	Univariate			Multivariate		
	p value*	odds ratio	95% CI	*p* value†	odds ratio	95% CI
TLR, high/low	0.030	10.7	1.4–82.0	0.031	17.0	1.8–435.4
Age, high/low	0.086	0.16	0.024–1.1			
Sex, male/female	0.59	2.5	0.2–32.8			
Etiology, virus/NBNC	1	0.8	0.14–4.5			
PLR, high/low	0.39	0.38	0.07–2.2			
NLR, high/low	0.39	0.38	0.07–2.2			
AFP, high/low	0.20	4.1	0.66–25.4			
DCP, high/low	0.67	1.8	0.32–10.2			
ALBI, G2/G1	0.086	6.2	0.94–41.4			
Intrahepatic main tumor size, ≥20 mm/<20 mm	0.21	–	–			
Intrahepatic tumor number, Multi/1	0.13	0.13	0.01–1.5			
MVI, yes/no	0.67	0.57	0.1–3.3			
N, 1/0	0.31	5.1	0.46–56.9			
M, 1/0	0.064	10.8	1.0–117.0	0.053	18.3	1.4–739.3
BCLC, C/A or B	0.39	2.7	0.43–16.4			

CI, confidence interval; TLR, tumor-to-liver ratio of the standardized uptake value; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy pro-thrombin; ALBI, albumin-bilirubin; TNM, tumor, node, metastasis; MVI, macroscopic portal vein invasion; BCLC, Barcelona Clinic Liver Cancer. *Fisher's exact test. †Multivariate logistic regression analysis.

assessed as complete response + partial response (PR). The disease control rate was assessed as ORR + stable disease. Progression-free survival (PFS) was defined as the time from the date of the first dose of the treatment to the date of death or the date of radiological evidence of tumor progression. Overall survival (OS) was defined as the time from the date of the first dose of the treatment to the date of death.

Statistical Analysis

Statistical analysis was performed using JMP Pro 16.0.0 (SAS Institute Inc., Cary, NC, USA). Intergroup differences were tested using the Mann-Whitney U test or the Fisher's exact test for continuous or categorical variables, respectively. For continuous values, the median value was used as a threshold if no specific cutoff had been established. PFS and OS were estimated using Kaplan-Meier methods, and differences among subgroups were evaluated using the log-rank test. All comparisons were considered significant if the p value <0.05.

Result

Overall Therapeutic Outcomes of the STRIDE Regimen

Patient baseline characteristics are shown in Table 1. In the radiological therapeutic response, the ORR and disease control rate in RECIST were 52.4% (11/21) and 71.4% (15/21), as shown in Figure 1a. There were no complete response cases. The median PFS (95% confidence interval [CI]) was 6.8 (4.0–not reached) months. Kaplan-Meier curve estimates of PFS are shown in Figure 1b. OS did not reach the median time during the observation period.

Factors Contributing to the Response on the 1st-Line Group

Comparing the response (PR) and the non-response groups (non-PR), higher TLRs were shown in the PR group compared with the non-PR group (median 2.6 and 1.5, respectively, $p = 0.032$), as shown in Figure 2a. The univariate analysis identified associations between TLR

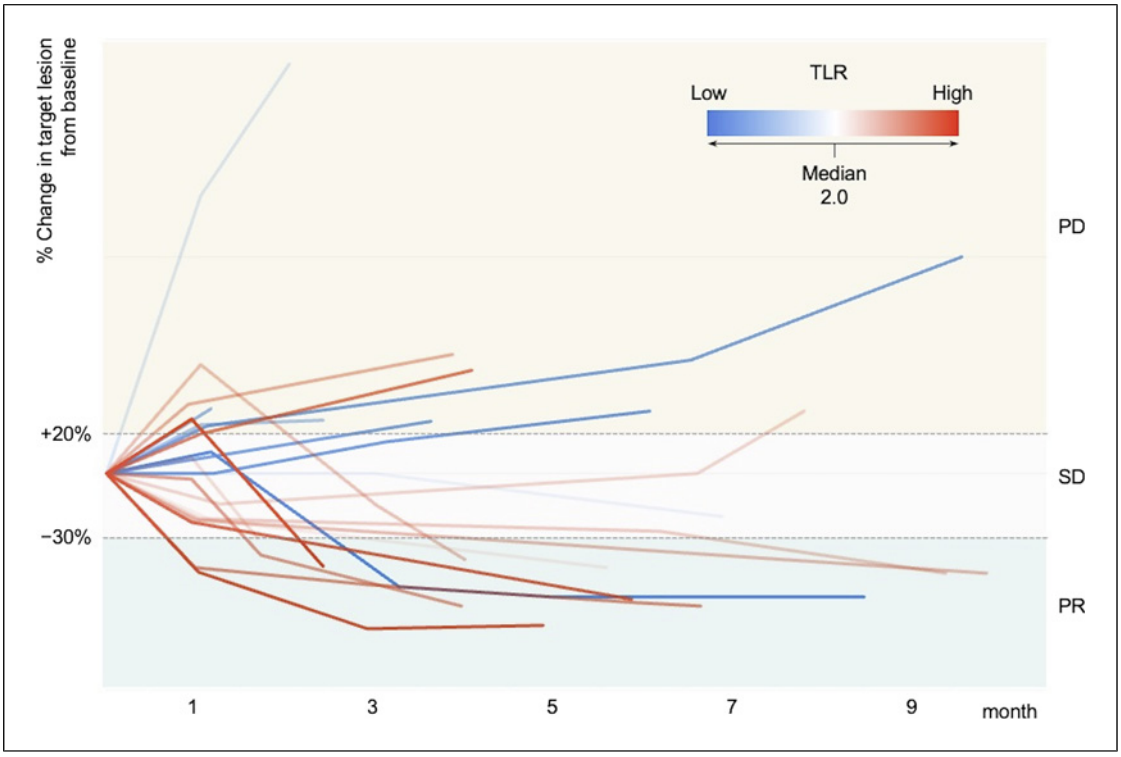


Fig. 3. The change in target lesion from baseline. A spider plot defined the change in target lesion from baseline according to RECIST 1.1. The line is shown in a blue-to-red gradient corresponding to the degree of TLR. PR, partial response; SD, stable disease; PD, progressive disease.

high/low (odds ratio = 10.7, 95% CI = 1.4–82.0, $p = 0.03$) (Table 2). Multivariable logistic regression analysis with TLR high/low and extrahepatic spread yes/no (M 1/0) identified TLR (odds ratio = 17.0, 95% CI = 1.8–435.4, $p = 0.031$) as an independent factor associated with PR (Table 2). We could obtain and evaluate the HCC tissues in 15/21 cases, and significantly higher TLRs were observed in the cases of poorly differentiated uHCC, known for its poor prognosis, compared with well-differentiated shown in Figure 2b. A spider plot colored by TLR showed the change in target lesion from baseline according to RECIST 1.1 (Fig. 3).

Discussion

Here, we reported that the STRIDE regimen for uHCC was effective in the 1st line, and a higher TLR on FDG-PET was suggested as a predictive factor for PR. Most FDG-PET-positive HCCs are poorly differentiated, as found in this study, and are biologically aggressive and known to have poor prognosis. Kudo et al. reported that Atezo/Bev therapy with lenvatinib-transcatheter arterial chemoembolization, ablation, or resection is expected to significantly improve the prognosis of FDG-PET-positive HCCs [8]. On the other hand, it has been reported that the greater the FDG accumulation on FDG-PET before starting Atezo/Bev therapy, the higher the PD rate [9]. The relationship between FDG-PET-positive status and the efficacy of immunotherapy for HCCs is controversial, but our findings suggest that HCCs with high TLR may benefit from STRIDE regimen in the ORR.

For patients undergoing anti-PD-1 inhibitor plus anti-CTLA-4 inhibitor combination therapy, a review summarizing the major clinical trials concluded that PD-L1 expression state can be a reliable biomarker for assessing ORR [10]. In HCC, it had been reported that a high SUVmax was significantly associated with PD-L1-positive expression [11, 12]. Taken together, we propose that baseline TLR could be a potentially useful biomarker for ORR for the STRIDE regimen. In the subgroup analysis of the HIMALAYA trial, the hazard ratios for OS compared with sorafenib were similar in cases positive or negative for PD-L1 expression, but long-term observation is needed to assess OS in our study.

Limitations

The main limitation of the current analysis is that it was a short-term study, with a small number of cases and a short observation period, so a longer-term study on a larger scale is needed. The ORR in this study was 52.4%, which was higher than the results of the HIMALAYA trial, but the small size study may have influenced these results.

Conclusion

A higher TLR on FDG-PET was suggested as a predictive factor for PR in the STRIDE regimen for uHCC. The association between FDG-PET and ICI treatment as an imaging biomarker for uHCC is worth further study. Predictive biomarkers to guide regimen selection and studies exploring regimen efficacy across broader subsets of patients remain a large unmet need.

Statement of Ethics

The study protocol was approved by the Hiroshima University Ethical Committee (Approval No. E2012-0726) in accordance with the Declaration of Helsinki [3]. All patients provided written informed consent.

Conflict of Interest Statement

Tomokazu Kawaoka received an honorarium from AstraZeneca K.K. and Chugai Pharmaceutical Co., Ltd.

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Author Contributions

Y.F. performed the analysis and wrote the paper. R.M., S.Y., K.Y., S.U., H.F., A.O., T.N., E.M., D.M., and M.T. were in charge of clinical data collection and recruited and monitored patients during follow-up. C.N.H. performed proofreading and edited the manuscript. H.N. provided guidance on the analysis. K.A. and Y.N. performed measurement of SUVmax on FDG-PET. S.O. and T.K. designed the study and supervised editing of the paper. All the authors read and approved the final manuscript.

Data Availability Statement

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

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