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Efficacy of Durvalumab-Tremelimumab Treatment in Combination With Locoregional Therapy in Unresectable Hepatocellular Carcinoma: A Preliminary Study

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Abstract

Background/Aim: Systemic therapy with immune checkpoint inhibitors for advanced hepatocellular carcinoma (HCC) treatment has demonstrated high response rates. Durvalumab plus tremelimumab (Dur/Tre) has been approved for HCC treatment and has become a first-line systemic therapy along with atezolizumab plus bevacizumab. However, there is early withdrawal owing to immune-related adverse effects, while others required sequential therapy owing to the lack of early therapeutic effects. Herein, we investigated the clinical characteristics of patients with progressive disease (PD) who were treated with Dur/Tre in addition to locoregional therapy.

Patients and Methods: We retrospectively evaluated eight patients with HCC, who were treated with Dur/Tre in March 2025 and continued Dur/Tre until PD was treated with locoregional therapy. Additionally, immunological changes, and treatment efficacy during continuation therapy were also assessed. Treatment efficacy was evaluated using modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Results: At Dur/Tre induction, patients (mean age, 76.88 years, all male) had alcoholic liver disease (n=3), nonalcoholic steatohepatitis (n=4), or hepatitis B virus (n=1). Six patients received Dur/Tre as first-line therapy, two were treated with atezolizumab plus bevacizumab as pretreatment, and the mean number of Dur/Tre cycles was 5.2. Neutrophil to lymphocyte ratio (NLR) was 2.14±1.51 at the time of Dur/Tre induction and worsened to 2.80±1.91 at the time of PD but significantly improved to 2.08±1.14 after locoregional therapy (p=0.047). Des-gamma-carboxy prothrombin (DCP) levels also decreased significantly after locoregional therapy (p=0.021). One patient responded partially, and seven achieved disease stability with continued treatment.

Conclusion: Continued Dur/Tre therapy may be effective in patients with improved NLR and DCP levels after adjunct locoregional therapy. Further studies involving larger patient cohort might determine strategic addition of locoregional therapy in PD.

Keywords: Unresectable hepatocellular carcinoma, Durvalumab–Tremelimumab, locoregional therapy, immune checkpoint inhibitors, STRIDE regimen.

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Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide, and reducing HCC mortality remains a major challenge (1). Systemic therapy is the first-line treatment for unresectable HCC (uHCC). The phase III HIMALAYA trial showed that the combination of durvalumab (an anti-PD-L1 inhibitor) and tremelimumab (an anti-CTLA4 inhibitor), known as the Single Regular Interval Durvalumab (STRIDE) regimen, was superior to sorafenib alone (2). The combination of immune checkpoint inhibitors (ICIs), durvalumab and tremelimumab (Dur/Tre) in the STRIDE regimen, is recommended as first-line therapy (3, 4). However, there is limited data to evaluate patient response. Early changes in lymphocyte counts and tumor markers may predict response to Dur/Tre (5). Studies have indicated poor responses in patients with a high neutrophil to lymphocyte ratio (NLR) (6). Although Dur/Tre in the STRIDE regimen offers potential for long-term responses, complete response (CR) is not elicited in all patients.

In this context, sequential therapy or alternative systemic therapies are in use. Studies have reported promising results on the safety and efficacy of locoregional therapy and systemic combination therapy as a downstaging strategy for preliminary uHCC (7-9). Achieving CR with systemic therapy alone remains challenging. Furthermore, there is no consensus on whether to switch to systemic pharmacotherapy or add locoregional therapy in non-CR patients, especially those with progressive disease (PD), where disease control is difficult and therapeutic advantage remains unclear. Although sequential systemic therapy is not always effective, adding locoregional therapy has been shown to prevent progression in patients showing early signs of PD after first-line treatment (10).

In this study, we investigated the usefulness of adding locoregional therapy to patients with PD during Dur/Tre treatment for uHCC and examined the clinical factors that influence prognosis.

Patients and Methods

Of the 23 patients with uHCC treated with Dur/Tre in the STRIDE regimen at Saiseikai Niigata Hospital between April 2023 and March 2025, we retrospectively studied eight patients who were treated with locoregional therapy instead of changing to systemic therapy when they decided on PD.

Treatment protocol. The patients received the STRIDE regimen, which consisted of a single 300 mg dose of tremelimumab (Tre) followed by 1,500 mg of durvalumab (Dur) every 4 weeks. Patients were treated until the occurrence of an unacceptable adverse event (AE) or PD was determined, at which point sequential treatment with locoregional therapy was selected and administered.

Response evaluation. Tumor response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (modified RECIST, mRECIST) (11) criteria, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Treatment-related AEs were evaluated according to the Common Terminology Criteria for Adverse Events (version 5) (12).

Ethics approval and informed consent. The study protocols were approved by the Institutional Review Board of the Saiseikai Niigata Hospital and were conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from all patients before participation in the study.

Statistical analysis. Categorical variables were expressed as numbers, and continuous variables as mean±standard deviation. Differences in quantitative values were analyzed using a Mann–Whitney *U*-test. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) (13). A two-tailed p-value of $p<0.05$ was considered statistically significant.

Table I. *Demographic characteristics of patients with unresectable hepatocellular carcinoma treated with durvalumab plus tremelimumab therapy at baseline.*

Categories	
Age (years)	76.88±8.43
Sex (male/female)	8/0
Etiology (Alc/NASH/HBV)	3/4/1
Child-Pugh (5/6)	5/3
Locoregional therapy (RFA/TACE RFA)	6/2
AFP (ng/ml)	3.60±2.19
DCP (mAU/ml)	89.13±50.38
Neutrocyte (/mm^3)	3101.25±1229.98
Lymphocyte (/mm^3)	1787.50±666.86
NLR	2.14±1.51
1st line/2nd line	6/2

Data are expressed as a mean±standard deviation or number. Alc: Alcohol; NASH: non-alcoholic steatohepatitis; HBV: hepatitis B virus; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; NLR: neutrophil-to-lymphocyte ratio.

Results

The patient backgrounds at the time of STRIDE (Dur/Tre) induction are shown in Table I. The mean age was 76.88±8.43 years, all patients were male, and Child-Pugh scores were 5 in five patients and 6 in three. The etiologies of alcohol, nonalcoholic steatohepatitis (NASH), and hepatitis B virus (HBV) were found in three, four and one patient, respectively. Dur/Tre was administered as the first-line treatment to six patients. The mean number of Dur/Tre cycles was 5.2. Two patients did not respond to atezolizumab/bevacizumab (Atez/Bev) and were switched to another therapy. Six patients received radiofrequency ablation (RFA) only, and two received transarterial chemoembolization (TACE) plus RFA for locoregional therapy. The alpha-fetoprotein level was 3.60±2.19 ng/ml, and the des-gamma-carboxy prothrombin (DCP) level was 89.13±50.38 mAU/ml (Table I).

The NLR was 2.80±1.91 at PD, which was worse than that (2.14±1.51) at the time of Dur/Tre induction, but significantly improved to 2.08±1.14 after locoregional therapy (p=0.047). DCP also worsened to 157.70±167.47 at PD from 89.13±50.38 at induction but improved to 54.98±48.71 by locoregional therapy (p=0.021). The remaining measurements did not show a significant difference before and after DT. These results led to a continued Dur/Tre treatment (Table II), PR in one patient, and SD in seven patients.

Adverse effects. No new AEs were observed in any of the eight patients during Dur/Tre therapy or add-on locoregional therapy (*i.e.*, super-selective TACE and RFA).

Discussion

In this study, we examined eight patients who opted for locoregional therapy instead of switching to systemic therapy upon PD. These patients were among the 23 patients with uHCC treated with the STRIDE regimen. The NLR at PD was worse than that at the time of Dur/Tre induction, but it significantly improved after locoregional therapy. DCP also worsened from Dur/Tre induction to PD but improved with locoregional therapy. This approach allowed continuation of Dur/Tre treatment. One patient achieved PR, and seven had SD, demonstrating the therapeutic benefit of locoregional therapy.

This study examined the significance of locoregional therapy administered during the STRIDE regimen for uHCC and identified immune boosts from locoregional therapy. In this context, locoregional therapies such as TACE and RFA are expected to enhance immune responses (14). However, the use of locoregional therapy in conjunction with immunotherapies for HCC has few reports.

Tumor markers are considered effective in determining the early response to treatment with Dur/Tre (5), and add-on therapy is considered necessary for patients who are unlikely to respond based on the tumor markers.

A critical issue in the treatment of HCC is achieving early response to therapy to improve the prognosis of patients who are unlikely to respond to Dur/Tre. Depending on the size and number of tumors, patients who have difficulty achieving CR with systemic therapy alone require multidisciplinary treatment combining systemic and local therapies, such as TACE and RFA.

This study suggests that the combination of Dur/Tre therapy and locoregional therapy (TACE and RFA) may

Table II. *Comparison of the change in variables among the following timepoints: before durvalumab plus tremelimumab therapy, progressive disease during durvalumab plus tremelimumab therapy, and after locoregional add-on therapy.*

Variables	Pre DT	PD during DT	After locoregional Tx	*p*-Value
AFP (ng/ml)	3.60±2.19	3.18±1.46	2.25±0.77	0.210
DCP (mAU/ml)	89.13±50.38	157.70±167.47	54.98±48.71	0.021
Neutrophils (/mm^3)	3,101.25±1,229.98	3,653.75±1,775.22	3,573.75±1,626.31	0.678
Lymphocytes (/mm^3)	1,787.50±666.86	1,648.75±730.68	1,956.25±641.16	0.139
NLR	2.14±1.51	2.80±1.91	2.08±1.14	0.047

PreDT: Before durvalumab plus tremelimumab therapy; PD during DT: progressive disease during durvalumab plus tremelimumab therapy; After Locoregional Tx: after locoregional add-on therapy; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; NLR: neutrophil-to-lymphocyte ratio.

improve the therapeutic efficacy of Dur/Tre therapy. This strategy is expected to create an immune-boosting environment in which therapeutic efficacy can be maintained, further prolonging the prognosis (14).

Given the multifaceted mechanisms promoting resistance to ICI in HCC, it is important to identify effective strategies to restore treatment sensitivity, including ICI therapy combined with other interventional therapies (15). Interventional therapy, a minimally invasive local treatment modality that encompasses TACE, ablation, and radiotherapy, is widely used in the management of HCC (15). RFA, in combination with ICI, has been shown to enhance the antitumor immune response by inducing the release of large amounts of tumor-associated antigens (16), thereby promoting an antitumor immune response (17, 18), and stimulating natural killer cell activation and differentiation (19).

As an equally effective locoregional therapy, TACE has been widely used in the treatment of various solid tumors and is the current standard of care for patients with intermediate HCC according to the Barcelona Clinic Liver Cancer (BCLC) guidelines (20). TACE induces tumor necrosis, inhibits the release of immunosuppressive factors, and alleviates immune function inhibition. Its embolic effect creates a hypoxic microenvironment, up-regulating hypoxia-inducible factor-1α (HIF-1α) expression and increasing programmed death (PD)-L1 expression on the surface of immune and tumor cells (21).

Furthermore, TACE is correlated with low levels of tumor-depleting CD8+PD-1+ effector and regulatory T cells, which may induce a shift from immunosuppression to immune-stimulation, thereby enhancing PD-1/PD-L1 inhibitor response (22). TACE also promotes tumor antigen release, altering the microenvironment to enhance ICI efficacy and strengthen antitumor immune responses. Therefore, TACE in combination with ICI enhances therapeutic efficacy by restoring immune function.

The combination of TACE and tremelimumab has been shown to be safe and feasible for advanced HCC, and combination therapy may increase immune cell infiltration within the tumor site (23). Buchalter *et al.* also evaluated whether day 1 administration of anti-CTLA4 leads to an enhanced immune response. They found that the combination of tremelimumab (day 1 only) and durvalumab plus TACE is safe and applicable in patients with HCC (24).

Currently, systemic therapy for HCC is evolving, and some kind of add-on therapy is expected to improve the therapeutic effect of the same systemic therapy and to prevent recurrence (25, 26). Locoregional therapy for PD patients treated with Dur/Tre in this study is one such example.

In order to combine locoregional therapy, patients must have good liver function, but Dur/Tre therapy can maintain liver function throughout the treatment period (27). Maintenance of liver function is critical for locoregional therapy in the management of HCC, even in PD patients with Dur/Tre. In this study, liver function reserve was maintained, and no serious adverse events were observed with combination locoregional therapy.

Study limitations. First, this is a retrospective study with inherent limitations. Second, the sample size is limited. Third, this is a single center study. However, there was no inter-institutional bias in the locoregional therapy of TACE and RFA.

Despite these limitations, our study provides further evidence supporting the tolerability and efficacy of adding locoregional therapy to Dur/Tre therapy for managing uHCC in the clinics.

Conclusion

In this study, we propose that the addition of locoregional therapy is effective for Dur/Tre cases with PD; however, further studies with larger patient cohorts are needed to determine whether the combinatorial TACE and RFA is more efficacious than the adjunct locoregional therapy.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

Conceptualization: Toru Ishikawa; Data Curation: Toru Ishikawa; Formal Analysis: Toru Ishikawa; Investigation: Toru Ishikawa, Ryo Sato, Hiroki Natsui, Takahiro Iwasawa, Masahiro Ogawa, Yuji Kobayashi, Toshifumi Sato, Junji Yokoyama and Terasu Honma; Methodology: Toru Ishikawa; Project Administration: Toru Ishikawa; Resources: Toru Ishikawa; Software: Toru Ishikawa; Visualization: Toru Ishikawa; Writing – Original Draft: Toru Ishikawa; Writing – Review & Editing: Toru Ishikawa, Ryo Sato, Hiroki Natsui, Takahiro Iwasawa, Masahiro Ogawa, Yuji Kobayashi, Toshifumi Sato, Junji Yokoyama, and Terasu Honma.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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