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ORIGINAL RESEARCH

Plasma Growth Hormone as a Prognostic Biomarker to Durvalumab and Tremelimumab in Patients with Advanced Hepatocellular Carcinoma

Shadi Chamseddine[1,*], Michael LaPelusa[2,*], Lianchun Xiao[3], Yehia I Mohamed[1], Sunyoung S Lee[1], Zishuo Ian Hu[1], Rikita I Hatia[4], Manal Hassan[4], James C Yao[1], Dan G Duda[5], Saumil Datar[6], Hesham M Amin[7,8], Ahmed O Kaseb[1]

[1]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Steele Laboratories, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [6]Department of Internal Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA; [7]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX, USA

*These authors contributed equally to this work

Correspondence: Hesham M Amin, Department of Hematopathology, The University of Texas MD Anderson Cancer Center, MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences Houston, TX, 77030, USA, Tel +1 713 794-1769, Fax +1 713 792-7273, Email hamin@mdanderson.org; Ahmed O Kaseb, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX, 77030, USA, Tel +1-713-792-2828, Fax +1 713-745-1163, Email akaseb@mdanderson.org

Introduction: In this study, we explored the potential of plasma growth hormone (GH) as a prognostic biomarker in patients with advanced HCC treated with durvalumab plus tremelimumab (D+T).

Methods: In this study, we included 16 patients with advanced HCC who received D+T at MD Anderson Cancer Center between 2022 and 2023 and had plasma GH measurements recorded before treatment. Plasma GH levels were measured from prospectively collected blood samples and were correlated with progression-free survival (PFS) and overall survival (OS). The cutoff for normal GH levels in women and men was defined as ≤3.7 μg/L and ≤0.9 μg/L, respectively. The Kaplan–Meier method was employed to compute the median OS and PFS, while the Log rank test was applied to compare the survival outcomes between the GH-high and GH-low groups.

Results: Sixteen patients were included in this analysis, two female and fourteen male, with a median age of 65.5 years. At the time of the analysis, the 6-month OS rate was 100% among GH-low patients (6 patients) and 30% among GH-high patients (10 patients). OS was significantly longer in GH-low patients (not evaluable) compared to GH-high patients (3.94 months) ($p = 0.030$). PFS was also significantly longer in GH-low patients (not evaluable) compared to the GH-high patients (1.87 months) ($p = 0.036$).

Conclusion: Plasma GH is a prognostic biomarker in patients with advanced HCC treated with D+T. Given the relatively small patient cohort size, this finding should be further validated in larger randomized clinical trials in advanced HCC patients.

Keywords: hepatocellular carcinoma, growth hormone, durvalumab, tremelimumab, overall survival, progression-free survival

Introduction

Globally, hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality.[1–3] More than 80% of patients with HCC are diagnosed at an advanced stage.[4] Most patients ultimately require systemic therapy as a consequence of being diagnosed with unresectable disease or recurrence after resection and locoregional therapies.[5]

Prior to 2020, multikinase inhibitors were approved as first-line treatment options for patients with unresectable HCC.[6] Since then, the combination of atezolizumab, an antibody against programmed death-ligand 1 (PD-L1), plus bevacizumab, an antibody against vascular endothelial growth factor (VEGF), was shown to improve overall survival

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(OS) compared to sorafenib, a multikinase inhibitor, among patients with untreated advanced HCC in the Phase III IMbrave 150 trial.[7] Soon after, the STRIDE regimen, which combines tremelimumab, an antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), with durvalumab, an antibody against programmed death-ligand 1 (PD-1), successfully achieved its primary endpoint of demonstrating a statistically significant improvement in OS when compared to sorafenib in patients with untreated advanced HCC in the phase III HIMALAYA trial.[8] Additionally, the STRIDE regimen showed higher objective response rates and prolonged time to deterioration of quality of life versus sorafenib.[8] While both atezolizumab plus bevacizumab and durvalumab plus tremelimumab (D+T) are approved by the Food and Drug Administration (FDA) in the first-line setting for patients with advanced HCC, these regimens have relatively different side effect profiles.[9] The presence or absence of comorbid conditions, such as esophageal varices at high risk for bleeding, is essential to consider when deciding on a first-line treatment regimen in these patients.

It is currently unknown which patients with advanced HCC benefit most from D+T. Growth hormone (GH)-mediated signaling has been linked to the development and progression of various types of cancer, including HCC.[10–12] Our working hypothesis and proposed model are that chronic liver disease and liver tissue insult decrease hepatic production of circulating insulin-like growth factor 1 (IGF-I) in HCC patients.[13] Under the physiologic conditions, the pituitary secretes GH that activates hepatic GHR to stimulate IGF-I release. In turn, IGF-I suppresses the release of GH from the pituitary. In HCC, hepatic secretion of IGF-I is reduced because of liver insult, and its negative feedback effect on GH production is diminished. The marked production of GH by the pituitary promotes HCC survival. Hence, antagonism of GH/GHR binding by pegvisomant, a specific blocker of GH/GHR signaling, suppresses HCC.[13] Our group has provided strong evidence of the potential therapeutic role of targeting GH/GH receptor (GHR) pathway in HCC, based on pre-clinical and clinical data.[13–15] Despite the availability of an FDA-approved anti-GH therapy, the rationale for targeting GH pathway has not been validated in any cancer, including HCC.

Notably, our group has most recently reported the significant prognostic role in patients with advanced HCC treated with atezolizumab plus bevacizumab and found that patients who present with higher baseline GH levels have worse clinical outcomes.[14] In the current study, we aimed to assess the association between baseline GH levels and survival in patients with advanced HCC who were treated with D+T.

Patients and Methods

This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center (MDACC; protocol RCR03-0289), and all enrolled patients provided written informed consent prior to study commencement. We prospectively collected and measured pre-treatment plasma GH levels in patients with advanced HCC who were treated with D+T. We subsequently analyzed the relationship between pre-D+T treatment GH levels and progression-free survival (PFS) and OS.

Patients received one dose of 300 mg of tremelimumab plus 1500 mg of durvalumab every four weeks. Treatment with durvalumab was continued until disease progression, death, or the development of intolerable adverse events (AEs). The study included adult patients with pathologically or radiologically confirmed HCC, as defined by the American College of Radiology, who were treated at MDACC. Patients' blood samples and epidemiologic and clinical data were collected, and plasma samples were analyzed retrospectively for GH level. Plasma GH levels were determined using a CLIA-approved enzyme-linked immunosorbent assay (ELISA). We stratified patients into high and low GH groups (GH-high cutoff for women, >3.7 μg/L; for men, >0.9 μg/L). Clinical and demographic data were extracted from medical records.

PFS was calculated from the date treatment with D+T commenced to the date of disease progression or death, whichever occurred first. OS was calculated from the date treatment with D+T commenced to the date of the last follow-up visit or the date of death. We utilized the Kaplan–Meier method to calculate the time-to-event outcomes and employed the Log rank test to compare OS and PFS between the GH-low and GH-high groups. R version 4.2.1 (2022, The R Foundation for Statistical Computing) was used for analysis.

Results

The study included 16 patients with advanced HCC who were treated with D+T at MDACC between October 2022 to October 2023 and had GH levels measured before the initiation of treatment. The median age was 65.5 years (range: 52 to 78 years), and 87.5% of patients were male. Thirteen (81.25%) patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1. Eight patients (50%) had Child-Pugh classification A cirrhosis, and 8 patients (50.2%) had Child-Pugh classification B cirrhosis. The demographic characteristics of the patients are presented in Table 1. At the time of the analysis, 6 of the 16 patients had died. The median follow-up time was 4.96 months (95% CI: 3.75, NE).

Table 1 Clinical Characteristics of Patients with Hepatocellular Carcinoma Treated with Durvalumab Plus Tremelimumab

Variable (16 Patients)	Levels	Frequency (%)
Age	51–60	2(12.5%)
	61–70	10(62.5%)
	71–80	4(25%)
Sex	Female	2(12.5%)
	Male	14(87.5%)
Race	Asian	4(25%)
	Hispanic	2(12.5%)
	Other	1(6.3%)
	White	9(56.3%)
History of Drinking Alcohol	No	9(56.3%)
	Yes	7(43.8%)
History of Tobacco Use	No	6(37.5%)
	Yes	10(62.5%)
Family History of Liver Cancer	No	14(87.5%)
	Yes	2(12.5%)
Personal History of non-HCC cancer	No	13(81.3%)
	Yes	3(18.8%)
Cirrhosis	No	4(25%)
	Yes	12(75%)
ECOG	0	1(6.3%)
	1	12(75%)
	2	3(18.8%)
Child Pugh Score	A	8(50%)
	B	8(50%)
Metastasis	Yes	16(100%)

Abbreviations: HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Oncology Group.

The GH-high and GH-low groups were balanced with regard to how many prior lines of therapy patients received. There was no significant difference between the mean number of lines of prior therapy between groups - The mean number of lines of prior therapy received was 1.60 among patients in the GH-high group and 2.67 in the GH-low group (p = 0.3328) (Table 2). There was a statistically significant difference between mean baseline GH levels in the GH-high group and GH-low group (3.77 μg/mL vs 0.31 μ/mL; p = 0.006).

There was no statistically significant difference between GH high and GH low groups in terms of ECOG score, presence of cirrhosis, or Child-Pugh scores (Table 3).

Six patients (37.5%) had disease progression upon treatment with D+T. No patients had a complete response, while two patients (12.5%) experienced a partial response according to the modified response evaluation criteria in solid tumors (mRECIST).

Progression-Free Survival

Twelve patients had progressive disease or died. The median PFS among all patients was 2.46 months (95% CI: 2.17, NA). Eight of the ten GH-high patients had disease progression or died, with a median PFS of 1.87 months (95% CI: 0.72, NE). Two of the six GH-low patients had disease progression or died, a median PFS that was not evaluable (3.75, NE). The GH-low patients had a longer median PFS than the GH-high patients (p = 0.036) (Table 4 and Figure 1).

Overall Survival

The estimated median OS among patients in the GH-high group was 3.94 months (95% CI: 0.76, NE). The median OS among patients in the GH-low group was not evaluable, as none of the six GH-low patients died. Patients with low GH level had a longer median OS than patients with high GH level (p = 0.030) (Table 4 and Figure 1).

Discussion

Here, we reveal the potential biomarker value of pretreatment GH levels in HCC patients treated with D+T. GH is a plasma biomarker that stands out for its affordability and ability to be measured non-invasively. Our data shows that

Table 2 Number of Lines of Systemic Therapy Prior to Durvalumab Plus Tremelimumab

GH Category	n	Mean ± Standard Deviation, Median (Range)	p-value
High	10	1.60 ± 1.71, 1.5 (0, 5)	0.3328
Low	6	2.67 ± 2.07, 2.5 (0, 5)	

Abbreviation: GH, growth hormone.

Table 3 Categorical Variables by GH High and Low

Variable	Levels	GH: High	GH: Low	p-value
Cirrhosis	No	2(20%)	2(33.3%)	0.6044
	Yes	8(80%)	4(66.7%)	
ECOG	0	0 (0%	1(16.7%)	0.217
	1	7(70%)	5(83.3%)	
	2	3(30%)	0(0%)	
Child Pugh Score	A	4(40%)	4(66.67%)	0.2821
	B	6(60%)	2(33.33%)	

Abbreviations: GH, growth hormone; ECOG, Eastern Cooperative Oncology Group.

Table 4 Comparison of PFS and OS Between GH-High and GH-Low Patients Who Received Durvalumab Plus Tremelimumab

GH	N=16	Event	Median (95% CI) Months	3-Month Rate	6-Month Rate	p-value
PFS						
High	10	8	1.87 (0.72, NE)	20% (10%, 80%)	NE	0.036
Low	6	2	NE (3.75, NE)	80 (50%, 100%)	50% (20%, 100%)	
OS						
High	10	6	3.94 (0.76, NE)	60% (30%-100%)	30% (10–90%)	0.030
Low	6	0	NE (NE, NE)	100% (100–100%)	100% (100–100%)	

Abbreviations: GH, growth hormone; PFS, progression-free survival; OS, overall survival; NE, not evaluable.

GH could function as a valuable addition to the existing set of prognostic factors in patients with advanced HCC. Based on these findings, baseline GH levels may serve as a valuable tool to identify which patients derive the most benefit from treatment with D+T. Moreover, GH may be a potential target to inhibit immunotherapy resistance in advanced HCC.

Mechanistically, GH-mediated signaling has been shown to play a role in the development and progression of HCC.[10,12] Forced expression of GH in HCC cell lines promotes cell proliferation, cell survival, cell migration, and invasion. In addition, forced expression of GH promotes cancer stem cell (CSC)-like properties of HCC cells.[10] GH activates STAT3 via JAK2 and promotes CSC-like behavior of HCC through STAT3-dependent inhibition of claudin-1 expression.[10,16] Additionally, chronic inflammation within the liver and subsequent fibrosis and cirrhosis result in a reduction of the liver's ability to produce circulating insulin-like growth factor-1 (IGF-I), which triggers increased secretion of GH by the pituitary gland in the absence of inhibitory signaling from IGF-I. This, in turn, amplifies the activation of the GH receptor by GH.[11,12]

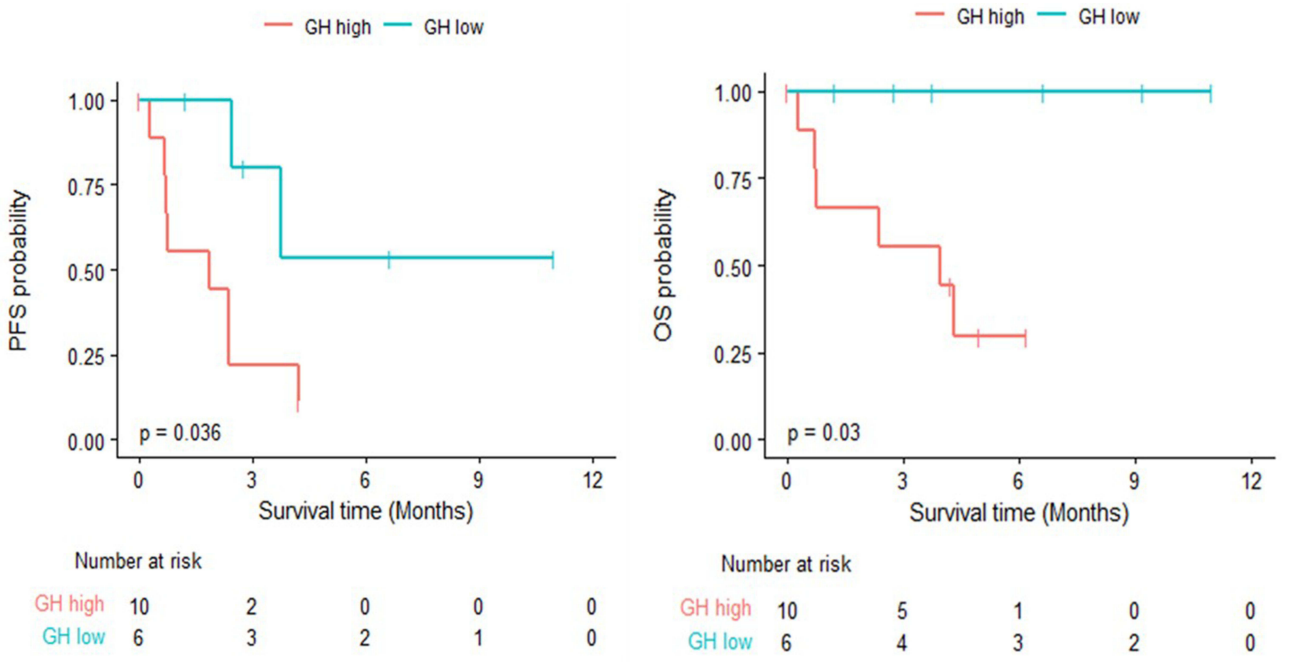

Figure 1 Kaplan–Meier curves representing PFS and OS among GH-high and GH-low patients who received durvalumab plus tremelimumab.
Abbreviations: GH, growth hormone; PFS, progression-free survival; OS, overall survival.

Despite the recent progress in treating patients with advanced HCC, there is still a significant need for dependable indicators that can accurately predict a patient's prognosis prior to treatment with immunotherapy. High plasma GH levels are associated with higher rates of vascular invasion, extensive liver disease burden, and more advanced Barcelona Clinic Liver Cancer and clinical (tumor, node, metastasis) staging.[13] Unsurprisingly, elevated baseline GH levels have been shown to be a marker of poor prognosis in patients with HCC.[13,16,17] Similar to our findings among patients treated with D+T, our group previously showed that patients with advanced HCC and elevated baseline GH levels have worse survival compared to patients with lower baseline GH levels upon treatment with atezolizumab plus bevacizumab.[17] The combination of these reports serves as rationale for exploring the feasibility of incorporating strategies to mitigate the ability of GH to induce and exacerbate carcinogenesis by utilizing GHR antagonists.[13]

Our study has several strengths. It identifies GH levels as a potential biomarker in HCC patients treated with D+T, contributing to the growing understanding of prognostic factors in this context. It also establishes a potentially beneficial biomarker which is affordable and non-invasive. Additionally, our data suggests that GH could serve as a valuable prognostic factor for patients with advanced HCC, providing clinicians with an enhanced toolset for risk stratification. Our study has limitations. It was carried out at a single center and involved a relatively small number of patients.

Conclusion

In conclusion, our study demonstrate that plasma GH represents a candidate biomarker for predicting treatment outcomes in patients with advanced HCC treated with D+T. Additional exploration, ideally through the implementation of large-scale, randomized clinical trials, complemented by correlative translational analyses and encompassing a more diverse representation of ethnicities, races, and genders, is imperative to unravel the significance of GH levels in individuals facing advanced HCC. While this study concentrated on the baseline prognostic value of GH levels, it is essential to recognize that serial assessments of plasma GH levels in forthcoming investigations hold the potential to furnish valuable data. This longitudinal approach may contribute to refining our understanding and, eventually, inform therapeutic decision-making in routine clinical practice. The inclusion of a broader spectrum of participants in future trials will not only enhance the generalizability of findings but also enable a more nuanced examination of the impact of GH levels across diverse demographic groups, thereby promoting a more personalized and equitable approach to the management of advanced HCC.

Ethics Approval and Informed Consent

The MD Anderson Cancer Center Institutional Review Board (IRB) approved the study and informed consent was obtained from the study participants prior to study commencement.

This study complies with the Declaration of Helsinki.

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Disclosure

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