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ORIGINAL ARTICLE

A new prognostic factor in patients with recurrent glioblastoma multiforme treated with bevacizumab plus irinotecan: Hemoglobin, albumin, lymphocytes and platelets (HALP) score

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Abstract

Background: In this study, we aimed to investigate whether hemoglobin, albumin, lymphocytes and platelets (HALP) score is a prognostic marker in bevacizumab plus irinotecan treatment in patients with recurrent glioblastoma multiforme (GBM).

Methods: Thirty-one patients were included in this study. The HALP score was calculated according to the formula: hemoglobin (g/L) x albumin (g/L) x lymphocytes (/L)/platelets (/L). The study population was divided into 2 groups (high-low) according to the HALP score. Overall survival (OS) and progression-free survival (PFS) of the two groups were compared.

Results: Median PFS and OS were 4.5 (0.9-14.9) and 8 (0.9-21.3) months, respectively. The median PFS of the low HALP score group was 1.85 (1.3-3.37) months, and of the high HALP score group was 4.96 (0.9-14.9) months (p=0.03). The OS of the high HALP score group (9.63 [7.28-11.9]) was statistically higher compared with the low HALP score group (2.26 [0.88-3.65]) (p<0.001). In multivariate Cox regression analysis, low HALP score was a significant poor prognostic factor for OS compared with high HALP score (HR: 0.063, p<0.001).

Conclusions: HALP score was determined as an independent prognostic factor for OS and PFS. Higher HALP score was associated with better OS and PFS.

Keywords: Bevacizumab, Biomarker, Glioblastoma, Prognosis.

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. The standard treatment approach is the combination of adjuvant radiation therapy with concurrent and adjuvant temozolomide following surgery. The median overall survival (OS) is 15 months, and even with the most appropriate treatment, most patients die within two years (1, 2).

GBM is a highly vascularized tumor that requires extensive collection of blood vessels to combat hypoxia. Vascular endothelial growth factor (VEGF)-mediated inhibition of angiogenesis by bevacizumab is a therapeutic strategy for GBM at the center of several clinical studies (3). A meta-analysis of 14 clinical studies showed that bevacizumab did not improve OS, but improved radiographic response rates and progression-free survival (PFS) in GBM, either as a single agent or in combination with chemotherapy (4). And it is currently only offered as salvage therapy for treatment-resistant cases. It has been shown that radiological imaging, clinical and laboratory parameters predict bevacizumab response in recurrent GBM (5-7).

Hemoglobin, albumin, lymphocyte, and platelet (HALP) score has been shown to be a new and potential prognostic indicator for various malignancies (8-17). This is the first study to investigate the prognostic significance of the HALP score in patients with recurrent GBM treated with bevacizumab plus irinotecan.

MATERIALS AND METHODS

In this retrospective study, all patients with a pathologically confirmed diagnosis of GBM followed in our clinic between April 2015 and July 2019 were examined. Patients who developed recurrence after adjuvant treatments and who received bevacizumab plus irinotecan in the first-line treatment were determined. Thirty-one patients whose hemoglobin, albumin, lymphocyte and platelet values could be reached at the beginning of the treatment and who received at least 3 cycles of this treatment and whose response was evaluated were included in the study. Since Isocitrate dehydrogenase mutation, 1p/19q co-deletion, O6-methylguanine-DNA methyltransferase could not be studied in our center, analysis could not be performed. This study was approved by the clinical research ethics committee of the Necmettin Erbakan University Meram Faculty of Medicine (Date: 17.07.2020 number: 2020/2749).

Albumin and hemogram levels before receiving treatment were recorded from the electronic files of the patients. The HALP score was calculated according to the formula: hemoglobin (HB) (g/L) x albumin (g/L) x lymphocytes (/L)/platelets (/L). PFS was defined as the time from the initiation of bevacizumab plus irinotecan to the first radiological progression, while OS was defined as the time from the initiation of therapy to death from any cause.

The optimal cut-off value of the HALP score was analyzed using X-tile software version 3.6.1 (Yale University, New Haven CT, USA). Kaplan-Meier method was used for survival analysis with the log-rank test used to statistical difference. A univariate Cox proportional hazards regression model was used to evaluate the prognostic value of each variable for OS. Multivariate Cox proportional hazards regression models were used to analyze independent prognostic factors. Homogenous variables in study groups according the HALP score were compared by independent samples t-test and expressed as mean ± standard deviation. Non-homogenous variables were compared by Mann-Whitney U test and expressed as median (minimum-maximum). Chi-square test or Fisher exact test was performed to comparison of categorical variables. A p value of <0.05 is considered as statistically significant. Data were analyzed by SPSS software. (SPSS 15.0; IBM Inc., Chicago, IL, USA).

RESULTS

Thirty-one patients were included the study, 5 (16%) were female and 26 (84%) were male. The mean age of all subjects was 46.3±12.2 years. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 22 (71%) patients was 1, and that of 9 (29%) patients was 2. Median follow-up time was 7.86 (0.33-21.3) months. 27 (87.1%) patients had received adjuvant temozolomide. Laboratory parameters were as follows; HB: 14.09 (11.2-18.6) g/dl, albumin 39.1 (29-49) g/L, lymphocyte 1.2 (0.2-2.70) 10^3/μL, platelet 229 (79-385) 10^9/L. Median PFS and OS were 4.5 (0.9-14.9) and 8 (0.9-21.3) months, respectively. The cut-off value for the HALP score for OS was 18 in analysis with using X-tile software (Figure 1). Those with a HALP score of 18 and below were defined as the low HALP score group, and those above 18 were defined as the high HALP

score group. Of the 31 patients, 13 had a low HALP score and 18 had a high HALP score. Age, gender, and ECOG-PS were not statistically different between the two groups (low and high HALP score group) (p=0.76, p=0.1,-p=0.12, respectively). There was no statistical difference between the histological type, residual tumor, tumor location, and surgery type low and high HALP score groups (p>0.05 for all, Table 1). The median PFS of the low HALP score group was 1.85 (1.3-3.37) months, and of the high HALP score group was 4.96 (0.9-14.9) months. This difference was statistically significant (p=0.03). The OS of the high HALP score group (9.63 [7.28-11.9]) was statistically higher compared with low HALP score group (2.26 [0.88-3.65]) (p<0.001).

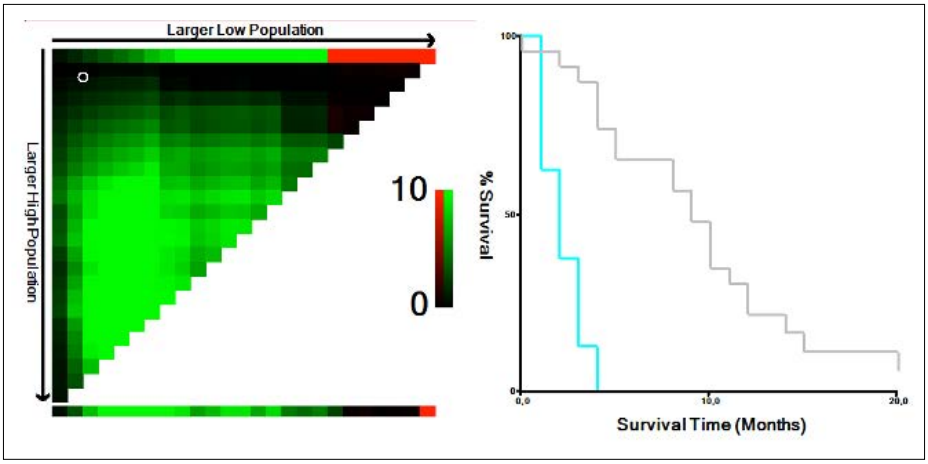

Figure 1: Cut- off values for the HALP score (hemoglobin, albumin, lymphocyte, and platelet) by X-tile software version 3.6.1.

Table 1: Demographic and clinical characteristics of the patients according to the HALP score. (HALP: hemoglobin, albumin, lymphocyte, and platelet)

≤18		The HALP score		
		>18	p	
Age (years) (mean ± st.d.)		47.5±12.7	45.9±12.2	0.76
Gender (n)	Female	4 (12.9)	1 (3.2)	0.01
	Male	4 (12.9)	22 (71)	
ECOG-PS (n)	1	4 (12.9)	18 (28.1)	0.12
	2	4 (12.9)	5 (16.1)	
Histological type (n)	GBM	6 (19.4)	20 (64.5)	0.42
	Secondary GBM	2 (6.5)	3 (9.7)	
Residual tumor (n)	No	2 (6.5)	11 (35.5)	0.41
	Yes	6 (19.4)	12 (38.7)	
Adjuvant temozolomide (n)	No	2 (6.5)	2 (6.5)	0.26
	Yes	6 (19.4)	21 (67.7)	
Progression free survival (month) (median[min-max])		1.85 (1.3-3.37)	4.96(0.9-14.9)	**0.03**

ECOG-PS: The Eastern Cooperative Oncology Group Performance Status. GBM: Glioblastoma multiforme.

Univariate analysis showed that HALP Score (≤18 vs >18), residual tumor (no vs. yes), and ECOG-PS (1 vs. 2) were important prognostic factors (Table 2). HALP Score was a significant prognostic factor; patients with low HALP score had a poorer prognosis than high HALP score (≤ 18 vs. >18; HR: 0.063, 95% CI: 0.016-0.249, p<0.001). The multivariate analysis showed that HALP score (p=0.003), and residual tumor (p=0.029) were significant prognostic factors. In multivariate Cox regression analysis, low HALP score was a significant poor prognostic factor for OS compared with high HALP score (≤ 18 vs. >18; HR: 0.063, 95% CI: 0.016-0.249, *p*<0.001) (Table 2).

Table 2: Univariate and multivariate analyses of overall survival in patients with brain tumor.

	Univariate analyses			Multivariate analyses		
Variable	HR	95% CI	p	HR	95% CI	p
HALP Score (≤18 / >18)	0.063	0.016-0.249	**<0.001**	0.077	0.015-0.408	**0.003**
Residual tumor (No/Yes)	3.445	1.449-8.192	**0.015**	2.69	0.222-3.646	**0.029**
Gender (F/M)	0.414	0.151-1.164	0.08	0.89	0.222-3.646	0.88
ECOG-PS (1/ 2)	3.07	1.230-7.680	**0.016**	2.14	0.841-5.492	0.11

F: female; M: male; HALP – hemoglobin, albumin, lymphocyte, and platelet; HR – hazard ratio; CI – confidence interval.

DISCUSSION

We found that the HALP score at the beginning of treatment in recurrent GBM patients treated with bevacizumab plus irinotecan is an independent prognostic factor for PFS and OS. PFS and OS were significantly shorter for patients in the low HALP score group than those in the high HALP score group.

As known, while hemoglobin and albumin levels are associated with the nutrition status of the body, lymphocytes and platelets are related to the immune system. The HALP score has been usually used to predict the prognosis of some types of cancers by using the character of showing the two main roles (inflammation and nutrition status) in the prognosis of cancer (16). Chen et al. firstly described this HALP score to predict the prognosis of gastric cancer. In 1332 patients with gastric cancer who underwent gastrectomy, the preoperative HALP ≥ 56.8 group had a significantly better prognosis than the HALP < 56.8 group (8). Also, the prognostic effectiveness of the HALP score has been investigated in, esophageal squamous cell cancer (9), pancreatic cancer (10), colorectal cancer (11), renal cell carcinoma (12), bladder cancer (13), prostate cancer (14, 15), and small cell lung cancer (16, 17). Low HALP score was associated with worse survival outcomes in all studied cancers. However, the optimum cut-off value was different in each study, so it is very important to define the optimal cut-off value of HALP score.

Bevacizumab, a humanized monoclonal IgG1 antibody, acts to bind to human VEGF and inhibit its activity (18). The objective response rate achieved with the combination of bevacizumab plus irinotecan in recurrent GBM is 38%, and the median PFS and OS are 5.6 and 9.2 months, respectively (19). Predictive factors of bevacizumab response in recurrent GBM have been investigated in several studies. In these studies, it has been shown that the development of hypertension and proteinuria, high eosinophil and lymphocyte levels, and low C-reactive protein (CRP)- to albumin ratio (CAR) and platelet to lymphocyte ratio (PLR) values due to bevacizumab treatment are predictive for better survival (6, 7, 20).

Inflammatory factors have been recognized as an important contributing factor to the complexity and lethality of GBM. Therefore, many studies are carried out considering that inflammatory factors may be prognostic factors for cancers, and the search continues. Previous studies have reported that tumor necrosis factor alpha and CRP are noticeably higher in patients with glioblastoma compared to healthy controls. However, the relationship between inflammatory factors and glioma risk or prognosis is controversial. There are positive and negative studies on this (21). A recent study showed that elevations

in all inflammatory markers were associated with poor OS in those using bevacizumab in recurrent GBM, but only elevated CAR and PLR were reported to be an independent predictive factor. The prognostic significance of the increase in neutrophil to lymphocyte ratio has not been demonstrated in this study (20).

This is the first study to show that the HALP score predicts the response to bevacizumab plus irinotecan treatment in patients with recurrent GBM. This score will be useful because it can be easily calculated with routine blood tests, is cheap and objective. If these results are confirmed by studies involving large patients group, they can be used in routine practice.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the Necmettin Erbakan University School of Medicine Ethical Committee (Approval date: 17.07.2020, Approval Number: 2020/2749).

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