High Expression of Glypican-1 Predicts Dissemination and Poor Prognosis in Glioblastomas

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■ OBJECTIVE: Glioblastoma (GBM) relapses locally or in a disseminated pattern and is highly resistant to chemo-radiotherapy. Although dissemination is associated with poor prognosis for patients with GBM, the clinicopathologic factors that promote dissemination have not been elucidated. Glypican-1 (GPC-1) is a heparin sulfate proteoglycan that is attached to the extracytoplasmic surface of the cell membrane and regulates cell motility. The aim of this study was to determine whether GPC-1 expression correlated with GBM dissemination and patient prognosis.

■ METHODS: GPC-1 expression was examined by immunohistochemistry in 53 patients with GBM who received radiotherapy and temozolomide treatment. We assessed the relationship between dissemination and clinicopathologic factors, including GPC-1 expression. We also evaluated the relationship between GPC-1 expression and overall survival (OS) by uni- and multivariate analyses of a range of clinicopathologic factors, including age, Karnofsky Performance Status, extent of resection, and O6-methylguanine-DNA methyltransferase (MGMT) status.

■ RESULTS: Logistic regression analysis revealed that GPC-1 expression correlated with dissemination ($P = 0.0116$). Log-rank tests revealed that age, Karnofsky Performance Status, extent of resection, MGMT status, dissemination ($P = 0.0008$) and GPC-1 expression ($P = 0.0011$) were significantly correlated with OS. Multivariate analysis indicated that age, MGMT status, and GPC-1 expression were significantly correlated with OS. GPC-1 expression had the highest hazard ratio (2.392) among all regressors.

■ CONCLUSIONS: GPC-1 expression significantly correlated with OS in patients with GBM who received radiotherapy and temozolomide treatment. GPC-1 expression can help predict the occurrence of dissemination and shorter OS in patients with GBM.

INTRODUCTION

The prognosis for patients with glioblastoma (GBM) remains poor, with a median survival of 12–15 months despite advanced surgery, radiotherapy, and chemotherapy.[1,2] Standard therapy for patients with primary GBM currently consists of surgery followed by radiotherapy with concurrent and adjuvant temozolomide (TMZ).[2] Patients treated with radiation and TMZ live 2.5 months longer than patients treated with radiation alone.[2] Almost all patients with GBM experience relapse, with tumors recurring locally or in a disseminated pattern intracranially or throughout the spinal axis. A 2016 study reported that dissemination occurred in up to 30% of patients with GBM, which was more frequent than the 8% dissemination

reported in a publication from a decade earlier.[3,4] The main reason for the difference in dissemination rates between the 2 reports is the advent of high-resolution magnetic resonance imaging, which has greatly improved the sensitivity of detection of disseminated disease. Although dissemination occurs in up to 30% of patients with GBM[3] and is a poor prognostic factor associated with a mean survival time of 3–4 months,[5-7] the clinicopathologic factors predisposing patients to the development of dissemination have not been elucidated.

Glypicans and syndecans are the 2 major families of heparin sulfate proteoglycans. Six glypicans have been identified in mammals and are referred to as glypican-1 through glypican-6.[8] Glypican-1 (GPC-1) is a ubiquitous protein that is attached to the extracytoplasmic surface of the cell membrane through a glycosyl-phosphatidylinositol (GPI) anchor. It plays important roles in many aspects of tumor behavior, including cell–cell and cell–extracellular matrix adhesion, metastatic potential, peritumoral invasion, angiogenesis, and mitogenic growth factor signaling, including fibroblast growth factor 2–regulated pathways.[7,9-16] GPC-1 is overexpressed in breast, pancreatic, esophageal cancers, and gliomas.[10,12,16-18] High expression of GPC-1 also is associated with poor prognosis for breast, pancreatic, and esophageal cancers.[12,16,17] However, to date there are no reports addressing the correlation between GPC-1 expression and prognosis for patients with GBM.

To improve the clinical management of GBMs, it is essential to accurately predict dissemination and prognosis. We hypothesized that GPC-1 expression was associated with metastatic potential and dissemination as the result of its important roles in cell–cell and cell–extracellular matrix adhesion. Therefore, this study aimed to evaluate GPC-1 expression in GBMs and to determine whether expression of GPC-1 is correlated with the occurrence of dissemination and the prognosis of GBM patients who received radiotherapy and TMZ treatment.

PATIENTS AND METHODS

Patient Selection

The records of 53 patients newly diagnosed with supratentorial GBM who underwent surgery, radiotherapy, and TMZ treatment at Hiroshima University Hospital from October 2005 to December 2015 were studied retrospectively. Tumors were diagnosed by 2 pathologists according to World Health Organization 2016 criteria.[19] The study population comprised 27 men and 26 women,

Table 1. Glypican-1 Expression and Clinicopathologic Characteristics

	Glypican-1 Expression		
	Positive	**Negative**	**P Value**
Number	27	26	
Age, years			
<60	11	14	0.3387
≥60	16	12	
Sex			
Male	15	14	0.4934
Female	12	12	
Karnofsky performance status			
<80	13	5	0.0243
≥80	14	21	
Extent of resection			
Total	12	14	0.4934
Partial and biopsy	15	12	
Second-line bevacizumab			
Yes	12	11	0.8753
No	15	15	
MGMT			
Positive	17	12	0.2180
Negative	10	14	
MIB-1 labeling index (mean, 40%)			
<40%	14	14	0.8844
≥40%	13	12	
IDH1 mutation			0.6104
Positive	1	2	
Negative	26	24	
Dissemination			0.0024
Yes	16	5	
No	11	21	

Statistical analyses were performed with the χ^2 test or Fisher exact tests.
MGMT, O6-methlguanine-DNA methyltransferase; IDH1, isocitrate dehydrogenase 1.

Table 2. Logistic Regression Analysis in Relation to the Presence of Dissemination

Regressor	Odds Ratio	95% CI	P Value
Age (<60 years vs. ≥60 years)	2.171	0.522–9.994	0.2884
Sex (male vs. female)	1.058	0.297–3.840	0.9308
KPS (≥80 vs. <80)	2.24	0.533–10.054	0.2703
Extent of resection			
Partial and biopsy vs. total	2.215	0.474–12.048	0.3174
Second-line bevacizumab (no vs. yes)	1.665	0.422–6.910	0.4663
MGMT (negative vs. positive)	1.073	0.266–4.336	0.9194
MIB-1 LI (<40% vs. ≥40%)	1.308	0.346–4.984	0.6887
GPC-1 (negative vs. positive)	5.091	1.429–20.687	0.0116

Statistical analysis was performed with logistic regression analysis.
CI, confidence interval; KPS, Karnofsky Performance Status; MGMT, O6-methlguanine-DNA methyltransferase; LI, labeling index; GPC-1, glypican-1.