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Prognostic significance of the markers IDH1 and YKL40 related to the subventricular zone

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Abstract

Glioblastoma multiforme (GBM), a highly aggressive brain cancer characterized by uncontrolled proliferation, resistance to cell death, angiogenesis, and vascular edema, remains one of the deadliest types of cancer. The subventricular zone (SVZ) harbors cells with great proliferative potential, and the microenvironment within the SVZ is permissive to growth and proliferation. This neurogenic niche is suspected to be a vulnerable site for the origin of subtypes of GBM. The aim of our study was to determine the immunohistochemical expression of mIDH1 and YKL40 in relationship to the SVZ of GBMs. YKL40, also known as chitinase-like protein 1, is included as a mesenchymal marker and associated with a poor prognosis. The protein is a secreted inflammatory molecule with no chitinolytic activity. However, the mutation of IDH1 (mIDH1) has been found in the cytoplasm and peroxisomes of 70-80% of secondary GBMs. In our study we found that YKL40-positive GBM is significantly linked to SVZ types IV and V ($p < 0.0001$). Our results show the diversity among GBMs related to the SVZ, which should be considered in the design of future targeted therapies. There was a significant impact of patient age, mIDH1 positivity, SVZ type III, and chemoradiotherapy on overall survival.

Key words: *glioblastoma, isocitrate dehydrogenase 1 mutation, YKL40 expression.*

Introduction

Glioblastoma multiforme (GBM), a highly aggressive brain cancer characterized by uncontrolled proliferation, resistance to cell death, angiogenesis, and vascular edema, remains one of the deadliest types of cancer [2,17,21]. The current standard of care involves aggressive surgery, radiation and chemotherapy, yet provides only a modest survival benefit [16, 27,37].

Based on cancer stem cell theory, and images of GBMs, recently there has been advanced a relevant classification related to the subventricular zone (SVZ) and its survival impact [18,22,24]. Since the SVZ harbors cells with great proliferative potential and the microenvironment within the SVZ is permis-

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sive to growth and proliferation, this neurogenic niche is suspected to be a vulnerable site for the origin of subtypes of GBM [13]. Recently, there has been a consensus about the subpopulation of cancer cells with stem cell characteristics, including self-renewal and multipotentiality; these cancer stem cells can propagate tumors *in vivo* [8,12]. Recent evidence suggests that tumor location plays an important role in prognosis and is likely related to the genetic profile of tumor cells of origin [18,30]. Furthermore, some authors have constructed prognostic models and analyzed probabilistic radiographic atlases of GBM phenotypes [11,13].

The GBM heterogeneity has motivated several studies to evaluate factors that predict prolonged survival for patients with GBM [4,18,20,24,38]. Such heterogeneity could be related, according to some authors, to the stem cell-like characteristics [24]. Lim *et al*. proposed a classification scheme that divides the GBMs into four groups by the spatial relationship of the contrast-enhancing lesion with the subventricular zone and cortex: type I – tumor in which the contrast-enhancing lesion contacts both the SVZ and the cortex; type II – tumor contacts the SVZ but not the cortex; type III – tumor contacts the cortex but not the SVZ; and type IV – tumor contacts neither the SVZ nor the cortex. Regarding the multifocal and/or multicentric GBMs there are many theories showing a close association with group I given the findings consistent with high migratory and invasiveness of cells, according to Willis' theory [24,33].

Based on recent studies [39], YKL40, also known as chitinase-like protein 1, is included as a mesenchymal marker and associated with a poor prognosis. The protein is a secreted inflammatory molecule with no chitinolytic activity [15] YKL40 has been postulated as a potential serum marker in glioblastoma [4,19] since it was found to have elevated levels in the serum of patients with GBM. However, the mutation of IDH1 (mIDH1) has been found in the cytoplasm and peroxisomes of 70-80% of secondary GBMs. mIDH1 is a selective marker for secondary glioblastoma supplementing clinical judgment to distinguish it from primary glioblastoma. There are few reports related to the mutated IDH1 expression and its subventricular zone relationship [11]. The aim of our study was to determine the immunohistochemical expression of mIDH1 and YKL40 in relationship to the SVZ of GBMs.

Material and methods

A retrospective study was performed on 204 GBMs operated on at the Neurosurgical Unit of Asturias Hospital, Spain, between December 2005 and September 2011. We divided the GBMs into five groups. The first four groups were selected accordingly to the Lim [24] classification. We then selected multifocal or multicentric presentation of GBMs as a fifth group.

Detailed data regarding clinical presentation, imaging features, surgical procedure, pathological analysis, oncological treatment, progression-free survival (PFS), and overall survival (OS) outcome were recorded. The extent of resection was determined by early postoperative MRI (within 48 hours). Subtotal and total resection were defined as those tumors with residual and no residual enhancement, respectively, achieved by comparing pre- and postoperative MRI. Extent of resection was classified as either total (> 95%), subtotal (< 95%) or biopsy by a neuroradiologist blinded to patient outcomes. Patients were informed of the investigational nature of this study and written informed consent was obtained from each patient in accordance with institutional guidelines. Patients with a Karnofsky Performance Scale (KPS) score ≥ 70 and age < 60 were included to receive conventional radiotherapy and chemotherapy after surgical resection: 1.8-2.0 Gy per day, over a period of 6 weeks, for a total dose of 60 Gy and temozolomide therapy at a dose of 75 mg/m^2 per day, seven days a week for 42 consecutive days during radiotherapy (as used in the EORTC study by Stupp *et al*.) [3,23,36].

The pathology was determined by a senior neuropathologist in all instances, and the grading criteria were based on the World Health Organization (WHO) classification system.

All statistical analyses were performed with SPSS Statistics version 20 (IBM) with a significance level of $p = 0.05$. Fisher's exact test was used for evaluation of the association between YKL40 and mIDH1 (with positive and negative expression) and covariates. Survival analysis was carried out with the Kaplan-Meier method and a log rank test. For multivariate analysis of OS and PFS, a Cox proportional hazards model was performed using age (< 65 vs. ≥ 65), gender, initial KPS score (< 70 vs. ≥ 70), hemisphere, subventricular relationship, extent of resection, and first line therapy as covariates. All tests were two-sided, and a p value of < 0.05 was con-

Table I. Patient characteristics

Factor	All patients (N = 204), n (%)
Median age at diagnosis (years) ± SD	63 ± 10.86
Range	26-85
Sex	
Male	115 (56.4)
Female	89 (43.6)
Karnofsky Performance Scale score	
< 70	30 (14.7)
≥ 70	174 (85.3)
Hemisphere	
Right	115 (56.4)
Left	89 (43.6)
Subventricular relationship	
Group I	18 (8.8)
Group II	35 (17.2)
Group III	75 (36.8)
Group IV	42 (29.6)
Group V	34 (16.7)
Surgery	
Gross total resection	44 (21.6)
Subtotal resection	119 (58.3)
Biopsy	41 (20.1)
First-line therapy	
Radiotherapy	36 (17.6)
Chemotherapy	1 (0.5)
Radiotherapy and chemotherapy	123 (60.3)
Therapeutic absention	44 (21.6)

sidered significant. The confidence intervals were calculated at the 95% level.

Results

The population of our study consisted of a total of 204 patients harboring GBMs. The baseline clinical data are summarized in Table I. Among the patients in the study, the median age was 63 ± 10.86 years. Most patients were male (115). The median initial KPS score was 80. Overall, for surgical resection, 44 patients underwent gross total resection (GTR), 119 patients underwent subtotal resection (STR), and 41 patients underwent biopsy. Although statistically significant ($p < 0.05$), there was not a greater extent of resection or more radiotherapy combined with chemotherapy, among mIDH1-positive GBMs.

In 94 patients, YKL-positive cells were identified. YKL40 expression was found predominately in the cytoplasm. YKL40 was strongly stained in all positive samples. One hundred and ten were YKL40 negative. In 42 patients the mIDH1 was positive. One hundred sixty-two were IDH1 negative.

The median OS was 34.64 weeks ± 45.5 and the median PFS was 15.35 ± 26.93 weeks. Kaplan-Meier estimates for OS by subventricular relationship are shown in Figures 2 and 3. The median OS (more than 54 weeks) after pathological diagnosis was higher in patients with mIDH1-positive GBMs (55.4%) than in those with YKL40-positive GBMs (23.2%) ($p > 0.001$ and $p > 0.05$, respectively). Long-term survival (LTS) was identified in 4 (66.7%) IDH1-positive GBMs. Long-term survival was identified in 1 (16.7%) YKL40-positive GBM (Table II). The median PFS among those with mIDH1-positive GBMs was higher than those with YKL40-positive GBMs (1 and 0, respectively).

Tumor location

All tumors were supratentorial in location. We did not find statistically significant differences between the right and left hemisphere linked to YKL40 and mIDH1 immunoexpression. Of 204 patients, 12 YKL40-positive GBMs and 3 mIDH1-positive GBMs had type I tumors; 16 YKL40-positive GBMs and 2 mIDH1-positive GBMs had type II tumors; 17 YKL40-positive GBMs and 33 mIDH1-positive GBMs had type III tumors; 29 YKL40-positive GBMs and 2 mIDH1-positive GBMs had type IV tumors, and 20 YKL40-positive GBMs and 2 mIDH1-positive GBMs had type V tumors.

Multivariate analysis

A multivariate proportional hazards model analysis, based on the forward stepwise selection technique, was used. The covariates significantly associated with improved OS were: younger age at diagnosis (hazard ratio [HR] = 1.44; 95% CI: 1.03-2.01, $p = 0.031$), type III and type I GBMs (HR = 0.46; 95% CI: 0.25-0.84, $p = 0.013$), and chemoradiothera-

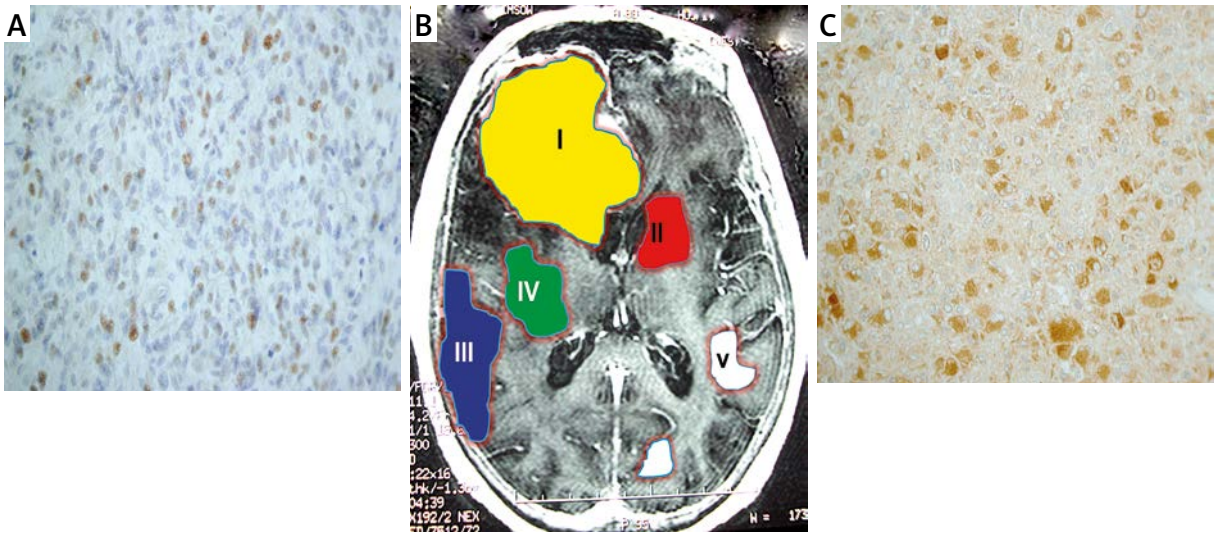

Fig. 1. Magnetic resonance imaging (**B**) and photomicrographs (**A** and **C**) of glioblastoma multiformes (GBM) in the present study. **A)** Immunohistochemical staining of mIDH1 showing classic histological features of GBM. mIDH1 has been found linked to group 3 in a large proportion of cases. **B)** Classification of GBM into groups I-IV [18,24], based on MRI, and the multifocal (V) group considered in our series. **C)** Immunohistochemical staining of YKL40.

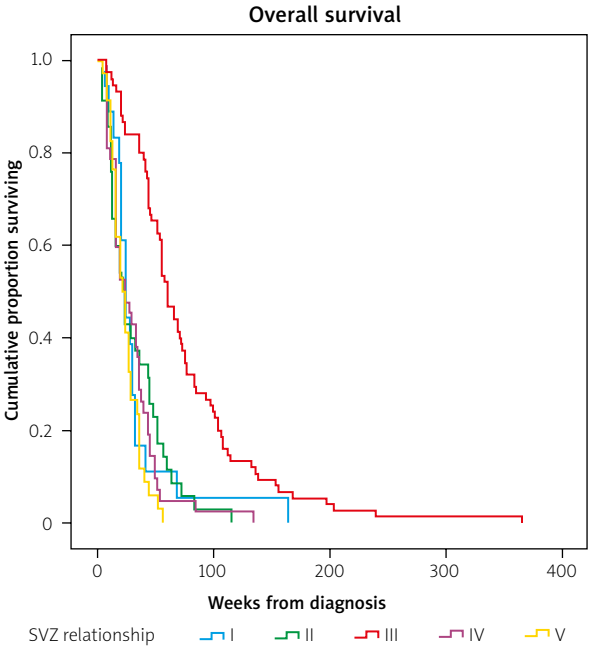

Fig. 2. Kaplan-Meier survival curves of overall survival categorized according to the subventricular zone relationship (log rank $p = 0.00$).

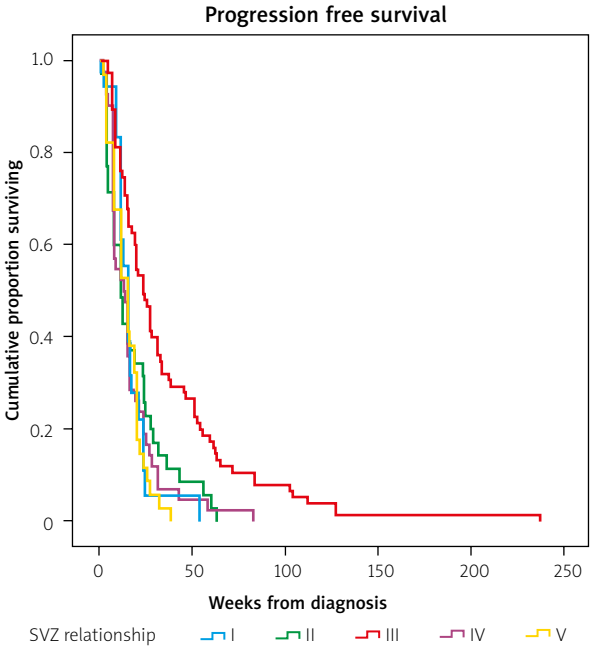

Fig. 3. Kaplan-Meier survival curves of progression-free survival categorized according to the subventricular zone relationship (log rank $p = 0.00$).

py (HR = 0.20; 95% CI: 0.12-0.33, $p = 0.000$) were the most independent factors linked to OS. The results of this model are given in Table III. In regards to PFS, good performance status (KPS) (HR = 0.48; 95% CI: 0.31-0.75, $p = 0.001$), mIDH1 (HR = 0.60; 95% CI: 0.40-0.90, $p = 0.015$), and chemoradiotherapy (HR = 0.33; 95% CI: 0.21-0.52, $p = 0.000$). Significantly more mIDH1- positive GBMs showed a relation with type III ($n = 33$; 44%) compared to YKL40-positive GBMs ($n = 17$; 22.7%).

Table II. Patient characteristic of the study population compared to YKL40 and mIDH1

Factor	YKL40+	YKL40–	Mutated IDH1+	Mutated IDH1–	*p* value YKL40/mIDH1
Age					< 0.0001
< 65	45 (38.1)	73 (61.9)	37 (31.4)	81 (68.6)	
≥ 65	49 (57)	37 (43)	5 (5.8)	81 (94.2)	
Sex					0.26/0.22
Male	57 (49.6)	58 (50.4)	20 (17.4)	95 (82.6)	
Female	37 (41.6)	52 (58.4)	22 (24.7)	67 (75.3)	
Karnofsky Performance Scale score					1.00/0.14
< 70	14 (46.7)	16 (53.3)	3 (10)	27 (90)	
≥ 70	80 (46)	94 (54)	39 (22.4)	135 (77.6)	
Hemisphere					0.11/0.60
Right	47 (40.9)	68 (59.1)	22 (19.1)	93 (80.9)	
Left	47 (52.8)	42 (47.2)	20 (22.5)	69 (77.5)	
Subventricular relationship					< 0.0001/< 0.0001
Group I	12 (66.7)	6 (33.3)	3 (16.7)	15 (83.3)	
Group II	16 (45.7)	19 (54.3)	2 (5.7)	33 (94.3)	
Group III	17 (22.7)	58 (77.3)	33 (44)	42 (56)	
Group IV	29 (69)	13 (31)	2 (4.8)	40 (95.2)	
Group V	20 (58.8)	14 (41.2)	2 (5.9)	32 (94.1)	
First-line therapy					0.005/< 0.0001
Radiotherapy	21 (58.3)	15 (41.7)	1 (2.8)	35 (97.2)	
Chemotherapy	0 (0)	1 (100)	0 (0)	1 (100)	
Radiotherapy and chemotherapy	45 (36.6)	78 (63.4)	40 (32.5)	83 (67.5)	
Therapeutic absention	28 (63.6)	16 (36.4)	1 (2.3)	43 (97.7)	
Surgery					0.003/0.03
Gross total resection	13 (29.5)	31 (70.5)	12 (27.3)	32 (72.7)	
Subtotal resection	54 (45.4)	65 (54.6)	27 (22.7)	92 (77.3)	
Biopsy	27 (65.9)	14 (34.1)	3 (7.3)	38 (92.7)	
Overall survival (weeks)					0.097/0.001
≤ 54	81 (55.1)	66 (44.9)	11 (7.5)	136 (92.5)	
> 162	1 (16.7)	5 (83.3)	4 (66.7)	2 (33.3)	
Progression-free survival (weeks)					1.000/0.174
≤ 54	90 (49.2)	93 (50.8)	31 (16.9)	152 (83.1)	
> 162	0 (0)	1 (100)	1 (100)	0 (0)	

Discussion

Patients diagnosed with GBM have a dismal prognosis [5]. Even though median survival is poor, individual survival is heterogeneous, with some patients surviving for several years [5,9,34]. Age at diagnosis, KPS score, and extent of resection have been the most well-documented predictors of survival. Age has consistently been shown to be one of the most powerful prognostic factors for survival in patients with GBM, with younger patients living much longer than older patients. Furthermore, the poor tolerance of older patients to aggressive toxic systemic chemotherapy often results in either treatment-related complications and/or suboptimal tumor treatment [10,28,31]. In the present study, we found a particularly strong tendency among young adults to harbor mIDH1-positive GBMs. Furthermore, Cox's regression model showed that younger patients were associated with better OS, consistent with previous published series [2,6,7,26]. Nevertheless, extent of resection remains a topic of debate, particularly for incomplete resections. The most comprehensive work to date on the value of extent of resection suggests that ≥ 98% is necessary to impact survival in patients with GBM [31,40]. In our study the extent of resection was not a prognostic factor in the Cox's regression model and in the characteristics linked to YKL40 and mIDH1 expression, judging by postoperative enhancing MRI rather than by the neurosurgeon himself may be the reason.

In the present study we found that YKL40-positive immunoexpression, reflecting the mesenchymal GBM subgroup [9,15,39], was not significant in the OS and PFS Cox's proportional hazards model. Interestingly, our data showed more YKL40-positive expression among subventricular contacting GBMs than mIDH1-positive GBMs. The expression of mIDH1 is associated with prolonged OS and PFS in a Cox's regression model, consistent with other population-based studies of GBMs [14,29,32,35,41]. The gross total resection and the radiotherapy combined with chemotherapy associations were not of prognostic value for either OS or PFS.

Recent evidence suggests that GBMs with both SVZ and cortical involvement and SVZ contact alone result

Table III. Multivariate analysis of factors associated with overall survival (OS) and progression-free survival (PFS) Cox's proportional hazards model with a forward stepwise approach

Factor	OS		PFS	
	p	HR (95% CI)	*p*	HR (95% CI)
Age (< 65 vs. ≥ 65)	0.031	1.44 (1.03-2.01)	0.265	1.18 (0.87-1.60)
Karnofsky Performance Scale score (< 70 vs. ≥ 70)	0.207	1.32 (0.85-2.04)	0.001	0.48 (0.31-0.75)
Gross total resection	0.390		0.248	
Subtotal resection	0.211	1.27 (0.87-1.86)	0.142	1.31 (0.91-1.89)
Biopsy	0.262	1.36 (0.79-2.32)	0.889	0.96 (0.54-1.69)
YKL40 (no vs. yes)	0.999	1.00 (0.71-1.40)		
Mutated IDH1 (no vs. yes)	0.028	0.62 (0.41-0.95)	0.015	0.60 (0.40-0.90)
Group I	0.011			
Group II	0.607	0.84 (0.45-1.59)		
Group III	0.013	0.46 (0.25-0.84)		
Group IV	0.886	1.04 (0.57-1.90)		
Group V	0.858	0.94 (0.49-1.79)		
Radiotherapy	0.000		0.000	
Chemotherapy	0.005	0.46 (0.27-0.79)	0.640	1.63 (0.21-12.66)
Radiotherapy and chemotherapy	0.000	0.20 (0.12-0.33)	0.000	0.33 (0.21-0.52)
Therapeutic absention	0.000	1.09 (0.53-0.17)	0.002	2.39 (1.38-4.14)

in shorter PFS and OS [13,18]. Interestingly, we found significantly more type III GBMs than the remaining groups among mIDH1-positive GBMs. mIDH1 positivity was more frequent in secondary GBMs than in primary GBMs (37 and 5, respectively). Of note, among YKL40-positive GBMs there were more type IV and V than type III GBMs. The main reasons for a less favorable outcome in GBM patients with SVZ involvement are not yet completely understood. Type IV and V were particularly linked to YKL40-positive GBMs. In our series we identified 34 (16.7%) type V GBMs. In the literature, the incidence of multiple lesions at the time of diagnosis ranged anywhere from 0.5 to 20% [14].

To the best of our knowledge, the immunoexpression of YKL40 has never been assessed in the GBMs associated with the subventricular zone. Since 2002 there have been published fewer papers addressing YKL40 and its expression in GBM, even though it seems related to radiotherapy resistance [15] and mesenchymal subtype, and inversely associated with EGFR. Additional studies concluded that patients with tumors adjacent to the SVZ were more likely to be multifocal at diagnosis and to have noncontiguous tumor recurrences [24]. YKL40 positivity contributes to progression of GBM through invasion, anchorage-independent growth and drug resistance [23].

Conclusions

According to the findings in the present study and the review of the literature, GBM is a highly aggressive tumor. Despite modest improvement in the OS of patients with GBM in the last decade, the outcome remains poor. Therefore, the need for more effective novel treatments in this neoplasm is urgently welcomed.

We demonstrate for the first time that YKL40 GBMs are significantly linked to SVZ types IV and V ($p < 0.0001$). However, it will be necessary to gain more information about its mechanisms of action in order to move forward with the use of YKL40 for potential application in glioma therapy. Our results show the diversity among GBMs related to the SVZ, which should be considered in the design of future targeted therapies. Age less than 65 years, mIDH1 positivity, type III GBMs, and temozolomide therapy are factors that independently predicted a prolonged OS. These results, however, may be limited by an inherent bias in patient selection, which may favor patients with more superficial tumors. We attempted to minimize the limitations by using strict inclusion criteria and Cox's proportional hazard model analysis. Therefore, despite this potential source of bias, these findings may help to guide treatment paradigms, prognosticate survival, and provide more information for GBM patients through the identification of these prognostic factors.

Disclosure

Authors report no conflict of interest.

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