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YKL-40 (CHI3-L1) A NOVEL PROGNOSTIC BIOMARKER IN WHO GRADE III ANAPLASTIC GLIOMAS

Pathology

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ABSTRACT

Introduction: YKL-40, also known as Chitinase-3-like protein 1 (CHI3L1), has been proposed as a novel prognostic biomarker in numerous cancers including gliomas. There are very few studies/ reports detailing the prognostic value of YKL-40 in WHO grade III anaplastic gliomas (AG), or its correlation with the clinically established diffuse glioma biomarkers; IDHmutation and 1p19q codeletion and the WHO 2016 histomolecular subgroups. In this study we evaluated the expression of YKL40 in AGs and assessed its prognostic significance in a single large cohort of Indian patients, within the diagnostic subgroups of AGs i.e., AO (1p19q codeleted and IDH mutant), AA IDHmutant and AA IDHwild type subgroups.

Methods: Immunohistochemistry was performed for YKL-40 expression on the retrospective cohort of anaplastic gliomas (AGs)(n=91), which had been molecularly stratified as AO,IDH mutant, 1p19q codeleted; AA IDH mutant and AA IDH wild type subgroups from our previous published study(1).

Results: YKL-40 immunopositivity was strong cytoplasmic with nil to weak nuclear staining of the tumor cells and was seen in 38 (41.76%) cases, whereas the remaining 53(58.24%) were negative, and although the majority of AO and AA IDHmutant lacked YKL-40 expression, all the AA IDHwild type tumors were YKL-40 positive. Further, YKL-40 immunopositivity had a statistically significant negative correlation with both the clinically established favorable prognostic markers 1p19q codeletion and IDH mutation and a very strong positive correlation with the IDHwild type genotype.YKL40 was associated with a shorter overall and recurrence free survival in AG patients($p<0.001$)

Conclusions: In conclusion, we show that YKL-40 is a marker of poor prognosis in AGs and all its subgroups. YKL-40 expression shows a negative correlation with IDH mutation and 1p19q codeletion and positive correlation with IDH wild type genotype, suggesting this marker to be biologically aggressive in AGs.

KEYWORDS

Anaplastic Gliomas, YKL-40 (CHI3-L1), Prognostic Biomarker.

INTRODUCTION

Gliomas are the most common type of primary brain neoplasms constituting about 30% of all central nervous system[CNS] tumours and 80% of all malignant brain tumours(2). The current WHO 2016 update classification of CNS tumors for the first time defines tumours by both histological and molecular parameters with the generation of an "integrated diagnosis "with the genotype trumping the histological phenotype in discordant cases. Accordingly, the diffuse WHO grade III anaplastic gliomas (AG) include anaplastic oligodendroglioma; Isocitrate dehydrogenase (IDH) mutant (IDHmut) and 1p19q codeleted (AO), anaplastic astrocytoma, IDHmutant (AA IDHmut), and anaplastic astrocytoma, IDH wild type (AA IDHwt). In our previous study(1), we had explored the prognostic significance of these histomolecular subgroups of AGs. Recently Chitinase like protein 1 (CHI3L1), also known as YKL-40, has been proposed as a novel prognostic biomarker in numerous cancers including gliomas–(317). Subsequent review of literature shows that, there were very few studies/ reports from India detailing the prognostic value of YKL-40 in gliomas.Some of the studies, including a previous study from our group, on YKL-40 have focused on a its significance in glioblastoma(GBM)(6). However, the expression of YKL40 in the histomolecular subgroups of AG or its correlation with the clinically established adult glioma biomarkers is not reported. Hence in this study, we studied the expression of YKL40 in AGs and assessed its prognostic significance in a single large cohort of Indian patients, within the diagnostic subgroups of AG ie., AO(1p19q codeleted and IDH mutant), AA IDHmut and AA IDHwt.

MATERIAL & METHODS:

This retrospective study was carried out on 91 adult patients diagnosed with AG. The patient selection, pathology review, methodology for immunohistochemistry(IHC) for IDH1(R132H), sequencing for IDH status, and Fluorescent in situ Hybridisation(FISH) for 1p19q chromosome copy number status, clinical data, and survival values has been published in our prior study(1).

IHC for YKL-40 expression was performed on 4µm Tissue Microarray (TMA) sections using anti-YKL-40 antibody [1:200, Santa Cruz Biotechnology, USA (C-18: sc-6001]. Briefly, following the initial processing steps, the slides were incubated overnight with the primary antibody. This was followed by incubation with secondary antibody (MACH1, Biocare medical) and 3, 3'-diaminobenzidine (Sigma-Aldrich, St Louis, Missouri, USA) was used as chromogenic substrate. We used primary GBM samples from our previous study as positive control and a negative control, in which the primary antibody is excluded, was incorporated with each batch of staining. Staining intensity was graded as +2 (strong positive staining), +1 (weak positive staining) & 0 (negative/ no staining), whereas the labeling index (LI) for YKL-40 was expressed as a percentage of cells that were positively stained (+2 staining intensity) among the total number of cells that were counted. In our study only a staining intensity of +2 i.e, strong positive staining was considered to label the tumor cells and LI > 10% cut off was considered as positive for YKL-40 expression as per previous studies(18-20)

STATISTICAL ANALYSIS

Data were analysed using the statistical software, IBM SPSS Statistics version 20. Variables were tested for normal distribution and non-parametric tests were used where required. Chi-square test was used to assess the molecular parameters and pathological distribution. Spearman rank correlation coefficient was used to assess significant associations between different molecular markers and AG subgroup alterations and inter-marker correlation. Overall survival (OS) and recurrence free survival (RFS) were analyzed using Kaplan-Meier survival curves. Factors that were significant in univariate analysis ($p<0.05$) were subjected to multivariate analysis (Cox regression models). Significant correlation between two parameters was taken at 95% confidence interval. All statistical tests were two-sided and the threshold for statistical significance was $p< 0.05$.

RESULTS

Patient cohort and molecular subgroups

The study cohort comprised 91 patients of AG, with a male to female (gender) ratio of 2.6:1. The median & mean age at diagnosis was 36.0 & 37.6+ 1.05 years respectively (range 19 to 64 years)(1). The median & mean follow up for the cohort from the date of reporting to our institute was 49.3&51.1+1.8 months with a range of 24.47 to 92.43 months.47(51.6%) of our patients had succumbed to the malignancy, whereas 23(25.3%) were alive and the remaining 21(23.1%) were lost to follow up at the time of analysis(1). These tumors had been earlier characterized molecularly using IHC for IDH1R132H and sequencing for other rare IDH1&2 mutations, and Fluorescent In situ Hybridiastion (FISH) for 1p19qcodeletion status(1).The histomolecular subgroups that were derived included 48 anaplastic oligodendrogliomas [AO], 35 anaplastic astrocytomas [AA IDHmut] and 8 AA IDHwt, constituting 52.7%, 38.5% and 8.8% of cases respectively(1).

2. Expression of YKL-40 in the histomolecular subgroups of AGs and Inter marker correlation

By IHC, YKL-40 expression was strong cytoplasmic with nil to weak nuclear staining of the tumor cells [Fig-1]. The frequency of YKL-40 expression across the diagnostic subgroups of AG is detailed in Table-1.

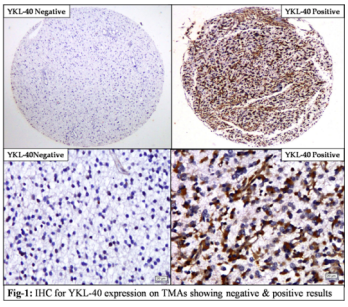

Fig-1: IHC for YKL-40 expression on TMAs showing negative & positive results

Table 1: Expression of YKL-40 in the WHO 2016 diagnostic subgroups Ags.

Expression of YKL-40	Integrated subgroups of AG: WHO 2016 classification (n=91)		
	AO (n=48) [IDH-mutant & 1p19q-codeleted]	**AA IDHmut**(n=35) [IDH-mutant& 1p19q Non-codeleted]	**AA IDHwt**(n=8) [IDH wild type& 1p19q Non-codeleted]
YKL-40 positive (n=38)(41.76 %)	14 (29.17%)	16 (45.71%)	8(100%)
YKL-40 negative (n=53) (58.24%)	34 (70.83%)	19 (54.29%)	Nil

Analysis for inter-marker correlation [Table-2] showed YKL-40 positivity to have a statistically significant negative correlation with both the clinically established good prognostic markers namely 1p19q codeletion (p=0.009& Rho= -0.270), and IDH mutation (p=0.001& Rho= -0.367), while it was positive in all the cases of AA IDHwt.

Table 2: Inter-marker correlation of the molecular markers in AGs **(n=91)**

Molecular markers	IDH		1p19q	
n=( )	**mut (83)**	**wt (8)**	**codeleted (48)**	**non-codeleted(43)**
YKL-40 Positive(38)	30	8	14	24
YKL-40 Negative(53)	53	0	34	19
p value	**0.001**		**0.009**	
Rho value	**-0.367**		**-0.270**	

3. Survival Analysis

On univariate survival analysis, YKL-40 positivity was associated with significantly reduced median OS & RFS when compared to YKL-40 negative tumors in all the diagnostic subgroups of AGs as well as in AGs as a group [Table-3].

Table 3: Influence of YKL-40 on median survival (in months) in subgroups of AGs & in AGs as a single group wrt to overall survival (OS) & recurrence free survival (RFS).

	AO (n=48)		**AAIDHmut** (n=35)		**AAIDHwt** (n=8)		**AG (n=91)**	
	OS	**RFS**	**OS**	**RFS**	**OS**	**RFS**	**OS**	**RFS**
YKL-40 positive (38)	61.3	58.2	35.1	26.2	30.2	24.0	38.6	31.7
YKL-40 negative* (53)	92.4	84.8	58.4	53.4	---	---	82.4	67.7
p value*	**<0.001**	**=0.041**	**<0.005**	**<0.001**	**---**	**---**	**<0.001**	**<0.001**

Note:*YKL-40expression was not seen in the AA-IDHwt group [ref Table-2]

DISCUSSION

YKL-40 also known as Chitinase-3-like protein 1 (CHI3L1), is a that is secreted glycoprotein approximately 40kDa in size that in humans is encoded by the CHI3L1 gene. The name YKL-40 is derived from the three N-terminal amino acids present on the secreted form and its molecular mass(21,22). YKL-40 is normally secreted by activated macrophages, chondrocytes, neutrophils and synovial cells. The exact physiological role of YKL-40 is not known but the protein is thought to play a role in the process of inflammation and tissue remodeling(23). YKL-40 is normally not expressed in non neoplastic glial tissue; therefore its expression in glial tumors seems specific. A few studies have shown YKL-40 to be capable of distinguishing anaplastic oligodendrogliomas from glioblastomas(24) and its expression in tumours has been shown to increase in a grade specific manner, being absent in normal brain and Grade II astrocytomas and with increasing expression in AA & Glioblastoma(6).In our study,YKL-40expression by IHC was predominantly cytoplasmic. Immunopositivity was seen in 41.76% cases in our study. Whilst the majority of AO and AA IDHmut lacked YKL-40 expression, all the AA IDHwt were YKL-40 positive. Our study showed YKL-40 immunopositivity to have a significant negative correlation with both the clinically established favorable prognostic markers; 1p19q codeletion and IDH mutation and a very strong positive correlation with the IDHwt genotypes. Although the IDHmut tumors are known to be a heterogeneous group, associated with varying clinical outcomes, the majority of IDHwt tumors are associated with a more aggressive clinical course(25,26) and our previous study had demonstrated this in the present cohort of patients(1). In this study we show association of YKL40 with worse clinical outcome as well as its strong positive correlation with the IDHwt tumors, thereby suggesting that YKL40 could serve as a poor prognostic marker in the group of AGs. These findings are supported by the findings in published literature where YKL-40 has been shown to facilitate migration of endothelial cells and promote the formation of branching tubules (27,28) and promote angiogenesis through vascular endothelial growth factor (VEGF)-dependent and independent pathways(29). In addition, YKL-40 has been shown to be directly produced by neoplastic cells, and act as a growth factor for connective tissue (5,30) and shown to have a potential role in tumour growth, invasion, angiogenesis and improved survival of glioma cells with poorer radiation response, chemoresistance, shorter time to progression and reduced overall survival in gliomas –(10,14,19,20,3148). Importantly, detection of YKL-40 in serum has been suggested as a marker for gliomas, and other cancers, to assess tumor grade and to monitor patients for recurrent tumour growth (3,12,16-19,34-46,50-56). Also numerous studies have postulated YKL-40 as a target for therapy in various malignancies (3,16,33,34,42,44,46,48,49,51). More recently, studies show that targeting YKL-40 with neutralizing antibodies has proved effective as a treatment in animal models of GBM and Wei Zhang et al in their study(57) showed that the polyphenolic natural product, Resveratrol represses YKL-40 expression by decreasing its promoter activity, mRNA transcription, and protein expression levels in U87 cells in vitro. These finding support the idea of targeting YKL-40 as a novel adjuvant therapy in glioma treatment and possibly enhance the effects of tumour excision, other adjuvant therapy and improve the prognosis for glioma patients.

Ours is probably the first study to define the prognostic impact of YKL-40 in AGs including the entire spectrum of the individual histological subgroups of AGs ie., AO, AA IDHmut and AA IDHwt.

CONCLUSION

In conclusion, we show that YKL-40 is a marker of poor prognosis in AGs and all its subgroups. YKL-40 expression shows a statistically significant negative correlation with both the clinically established favorable prognostic markers 1p19q codeletion and IDH mutation and a very strong positive association with the IDHwild type genotype which might help explain the biological aggressiveness of these subset of tumors. Validations on other independent and larger cohorts of diffuse gliomas would further strengthen the findings of our study.

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DISCLOSURE

1. Conflict of interest:

All the authors disclose that there is no conflict of interest relevant to the subject matter under consideration in this article. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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