Clinical and molecular factors of survival in Moroccan patients with Glioblastoma

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Introduction

Glioblastoma (GBM) is the most frequent and aggressive primary brain tumor despite aggressive treatement [3,4]. Primary GBMs, arise mostly in older age groups, with shorter survival time, and are more frequently compared to secondary GBMs [2]. The prognosis remains poor with a median survival of 9 to 15 months [1]. Several factors have already been studied. Indeed, younger age, good Karnofsky performance status (KPS), radio-chemotherapy, extent of tumor resection, histology and subtype of GBM have been identified as potential prognostic factors [3]. We analyzed TP53 and IDH1-2 genes in 34 primary GBM among 89Moroccan GBM patients to clarify the prognostic value.

Materials and methods

We conducted a retrospective analysis of 89 patients with newly diagnosed GBM between January 2004 and June 2010 (WHO guidelines). Variables analyzed were studied in table1. TP53 and IDH1-2 mutation.

Molecular Analysis

In 34 cases of GBM, DNA was extracted from tumor and blood samples. The screening of TP53, IDH1 and IDH2 genes were carried out by automated sequencing. PCR was done in a total volume of 15 ÂµL. PCR reactions were performed using the following primers: forward 5'-AATGAGCTCTATATGCCATCACTG-3' and reverse 5'-TTCATACCTTGCTTAATGGGTGT-3' for IDH1; forward 5'TGCACTCTAGACTCTACTGCC-3' and reverse 5'ACAAAGTCTGTGGCCTTGTAC-3' for IDH2. The sequences were analyzed by comparison to the consensus data of TP53, IDH1, and IDH2 genes using the GenBank accession numbers NM_000546.4, NM_005896.2, and NM_002168.2, respectively.

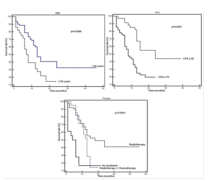
Results

The median age was 52 years. The median KPS was 70. The mean of clinical history delay was 3.84 months and the tumor size median was 44 cm3. Total tumor resection was performed in 12 cases (13.48%). Overall median survival was 12 months (95% CI: 9-13) for all patient (tableau1).

The TP53 analysis revealed three mutations 8.82 % (3/34). Two of these mutations affected exon 8, and one exon 5. The screening for IDH1 and IDH2 mutations revealed the absence of these mutations in our patients.Univariate analysis of prognostic parameters showed favorable prognostic value for overall survival of patients age<60 years, patient pre-operative KPS>80 compared to KPS<80 and radiotherapy (figure 1: Kaplan-Meier survival curves for significant prognostic factors).

Tableau1

figure 1



Prognostic factors	Sub-groups	No.	Median survival (months)	Log-rank test (p-value)	Cox regression analysis (p-value)	Hazard ratio (95% CI)
Age (years)	< 60	61	13	0.0088	NS	
	≥ 60	28	7.5			
Gender	Male	54	13	0.3111	NS	
	Female	35	11			
KPS	< 80	55	8	0.0001	0.0014	2.8000 (1.4930-5.2513)
	≥ 80	34	24			
Extent of surgery	Biopsy	31	12	0.2445	NS	
	Partial	23	13			
	Subtotal	23	11			
	Total	12	14			
Clinical history delay*	≤ 3	58	12	0.4901	NS	
	> 3	31	13			
Tumor size (cm^3)	≤ 40	39	12	0.5013	0.0240#	0.9904 (0.9822-0.9987)
	>40	43	13			
Treatment	RT	50	18	< 0.0001	< 0.0001	4.2094 (2.1384-8.2862)
	RT + CHT	21	13			
	No	18	5			

#: The tumor size parameter was entered as a continuous covariate in Cox regression analysis
*: Time (in months) between onset of the first clinical symptoms and diagnosis of Glioblastoma
NS: Not significant. KPS: Karnofsky Performance Score. RT: radiotherapy. CHT: Chemotherapy. No: non-treatment

Discussion

Four subtypes of GBM were identified. 1) Classical subtype characterized by aberrant EGFR activity and loss of chromosome 10. 2) Mesenchymal subtype characterized by alterations in the gene for NF1 and PTEN deletions. 3) Proneural subtype characterized by alterations in TP53, platelet-derived growth factor receptor (PDGFR), and IDH1. 4) Neural subtype gene expression pattern is the most similar to that of normal brain tissue (1.2). Despite aggressive treatment median survival time for patients with GBM is only 14.6 months (1.3). Intraoperative MRI have enabled improved radiographic and functional outcomes, yet still present major drawbacks. Intraoperative fluorescence imaging offers the potential to improve the extent of resection (4.5). The novel approaches include molecularly targeted therapies, immunotherapies, and gene therapy (6.7). This suggests that no single therapy will be efficacious across all subtypes.

Conclusions :

We showed the strong prognostic value of age, performance score, and radiotherapy, validating the results published in previous studies. This work could contribute towards informing further research on prognostic variables for patients with glioblastoma.

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