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Research Article

The relationship between IDH, P53 mutations, MGMT methylation with characteristics in high grade glioma patients

La relación entre IDH, mutaciones P53, metilación de MGMT con las características de pacientes con glioma de alto grado

Tran Anh Duc[1] https://orcid.org/0000-0002-2355-2006

Nguyen Van Ba[2] https://orcid.org/0000-0001-8603-2035

Nguyen Thanh Bac[1] https://orcid.org/0000-0002-8316-3088

Vu Van Hoe[1] https://orcid.org/0000-0002-2584-861X

Nguyen Duc Lien[3]* https://orcid.org/0000-0001-7568-1857

[1]Vietnam Military Medical University. Military Hospital 103. Department of Neurosurgery. Hanoi, Vietnam.

[2]Vietnam Military Medical University. Military Hospital 103. Oncology Center. Hanoi, Vietnam.

[3]Vietnam National Cancer Hospital. Department of Neurosurgery. Hanoi, Vietnam

*Author for correspondence. Email: drduclien@gmail.com

ABSTRACT

Introduction: Some gene mutations in high grade glioma patients have many implications in prognosis and treatment response.

Objectives: To describe the characteristics and associations of IDH, TP53 gene mutations and MGMT methylation status with some characteristics and treatment response in patients with high grade glioma.

Methods: A descriptive, prospective, uncontrolled study was conducted, in 52 patients with high-grade glioma. Research variables include age, sex, Karnofsky score, the rate of IDH, P53 mutation,


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MGMT methylation; the relationship between genes mutation with some characteristics and response to treatment according to the RECIST classification.

Results: For IDH gene mutation, grade III patients (23.1%) have a higher positive rate than grade IV (11.5 %); for P53 gene mutation, grade III patients (55.6 %) have a higher positive rate than grade IV (44.1 %); the rate of MGMT promoter methylation occurred in the study group of patients with the rate of 42.3 %. There is a relationship between IDH gene mutation with pathological results and malignancy in studied patients. Patients with the mutant expression of the IDH gene, p53, MGMT methylation status had better RECIST responses than patients without these expressions.

Conclusion: High-grade glioma mainly occurs in men, over 40 years old. The presence of mutations in IDH, P53 genes, and MGMT methylation status was a beneficial factor for treatment response as assessed by RECIST.

Keywords: mutant IDH; mutant TP53; MGMT methylation; high grade glioma.

RESUMEN

Introducción: Algunas mutaciones genéticas en pacientes con glioma de alto grado tienen implicaciones en el pronóstico y respuesta al tratamiento.

Objetivos: Describir las características y asociaciones de IDH, mutaciones del gen TP53 y estado de metilación de MGMT con algunas características y respuesta al tratamiento en pacientes con glioma de alto grado.

Métodos: Se realizó un estudio descriptivo, prospectivo no controlado, en 52 pacientes con glioma de alto grado. Las variables investigadas fueron: edad, sexo, puntuación de Karnofsky, tasa de IDH, mutación P53, estado de metilación de MGMT, relación entre la mutación de genes con algunas características y la respuesta al tratamiento según la clasificación RECIST.

Resultados: Mutación del gen IDH: los pacientes grado III (23,1 %) tienen una tasa positiva más alta que los grado IV (11,5 %). Mutación del gen P53: los grado III (55,6 %) tienen una tasa positiva más alta que los grado IV (44,1 %). La tasa de metilación del promotor de MGMT se produjo con una tasa del 42,3 %. Existe relación entre la mutación del gen IDH con los resultados patológicos y la malignidad. Los pacientes con la expresión mutante del gen IDH, p53, estado de metilación de


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MGMT tuvieron mejores respuestas RECIST.

Conclusión: El glioma de alto grado se presenta principalmente en hombres, mayores de 40 años. La presencia de mutaciones en los genes IDH, P53 y el estado de metilación de MGMT fue un factor beneficioso para la respuesta al tratamiento según lo evaluado por RECIST.

Palabras clave: IDH mutante; TP53 mutante; metilación de MGMT; glioma de alto grado.

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INTRODUCTION

Glioma is a primary brain tumor of the central nervous system accounting for about 27 % of intracranial tumors and 80 % of brain malignancies; up to 75 % of gliomas with astrocyte origin, of which high-grade glioma accounts for 78 %.[1] Only about 2 % of glioma cases progress to cancer, yet the treatment of high-grade malignant glioma has become the biggest challenge for oncologists. Despite advances in treatment, these tumors are still associated with higher morbidity and mortality, and shorter median survival than other cancers.[2]

In the past, surgery combined with radiation therapy was the standard treatment for patients with high-grade glioma (HGG). Recently, the combination of surgery, radiotherapy, and chemotherapy with temozolomide (TMZ) has shown superior results compared with radiation therapy alone in the treatment of newly diagnosed high-grade glioma in adults.[3]

Due to the limitations of current therapies for high-grade gliomas, the field of molecular biology has made significant advances in the past years in contributing to the diagnosis, identify novel treatments and prognosis for patients with HGG. Molecular characterization studies have confirmed that HGG modifications are complex and result from dysfunction of many different regulatory pathways in vivo and between them are closely related.[4]

Simultaneously in patients with HGG there are complex chromosomal and genetic alterations that


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lead to inactivation of various tumor suppressor genes, as well as aberrant activation of proto-oncogenes. It is necessary to conduct research on gene mutations in HGG patients that have many prognostic implications and their role in treatment response, thereby serving as the basis for research into targeted treatment of HGG disease, and it is very necessary for clinicians to give the best prognosis and treatment direction for patients with high-grade glioma.

Therefore, this study was conducted with the aim of describing the characteristics and associations of IDH, TP53 gene mutations and O(6)-methylguanine-DNA methyltransferase (MGMT) methylation status with some clinical, subclinical characteristics and treatment response in patients with high-grade glioma (HGG).

METHODS

Were included 52 patients with high-grade glioma undergoing surgery, histopathological diagnosis, immunohistochemistry, molecular biology tests, gene sequencing to identify mutations (IDH1, IDH2, p53, MGMT promoter methylation status) and combination chemotherapy and radiotherapy, at Vietnam National Cancer Hospital, Tan Trieu campus, Vietnam, from January 2019 to December 2020.

Selection criteria:

- Patients who were diagnosed as a high-grade glioma based on clinical symptoms and contrast-enhanced magnetic resonance imaging, histopathology.
- Received microsurgery to remove tumor and combined chemotherapy and radiation treatment.
- No life-threatening acute or chronic diseases.
- Informed consent to participate in the study.

Research design: descriptive, prospective, non-controlled study.

Research sample size: convenient sample was choosed.


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Variables studied: Karrnofski's score; pathology results and malignancy; the rate of mutations in IDH, P53 genes and determine MGMT methylation status; the relationship between IDH, P53 gene mutations, MGMT promoter methylation status with age, sex, histopathological results, Karnofsky score, response to treatment according to response evaluation criteria in solid tumours (RECIST) classification.

RECIST response assessment criteria were:[5]

- Fully responsive: tumor completely disappeared after 4 weeks.
- Partial responsive: > 30 % reduction in total tumor volume and no new tumor appearance after 4 weeks.
- Stable disease: tumor decreased in size < 30 % or increased in size < 20 % of total tumor.
- Progressive disease: tumor increased in size > 20 % of total tumor.

Criteria for assessing tumor response:

- After 6 months of surgery, the patient underwent concurrent chemoradiotherapy and was receiving additional chemotherapy according to the Stupp protocol,[3] assessing the objective response to treatment according to RECIST criteria.
- Evaluation of response based on comparison of magnetic resonance before and after surgery, 6 months of treatment in each patient.
- Evaluation of response was based on comparison of tumor size before and after treatment in each patient.

Data management and analysis: data were analyzed with SPSS 22.0 software, using descriptive statistics algorithms, calculating the mean and standard deviation, using the Chi-square test and Fisher's exact test to compare the difference between the presence or absence of mutations with the criteria to be investigated in terms of clinical, subclinical and RECIST classification. Any variable with $p< 0.05$ was considered to be statistically significant.

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From the ethical point of view, the confidentiality of the identity of the patients is maintained, only used for analysis as a group.

RESULTS

Demographic and some characteristics of patients

The average age of the study sample was 45.2 ± 14.4 years old, in which the most common age group was from 40 to 49 years old, accounting for 26.9 % and the lowest age was 7 years old, and the highest was 70 (table 1).

At the same time, there were more men than women with the corresponding rate of 61.5 % (32 patients) compared with 38.5 % (20 patients) (ratio 1.6:1, 0).

Karnofsky scores of study subjects upon admission were mainly in group I (42.3 %) and group II (34.6 %). Only 12 patients (23.1 %) belonged to group III. The mean Karnofsky score of the patients was 68.5 ± 14.7.

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Table 1 – Age characteristics and Karnofsky score of study subjects at hospital admission

Characteristics	Number of patients	Ratio (%)
Age groups		
< 18	3	5.8
18 - 39	14	26.9
40 - 49	14	26.9
50 - 59	13	25.0
60 - 69	6	11.5
≥ 70	2	3.8
Total	52	100
$\bar{X}$ ± SD	45.2 ± 14.4	
Max – Min	70 - 7	
Karnofsky score		
Group I (100 - 80)	22	42.3
Group II (70 - 60)	18	34.6
Group III (50 - 40)	12	23.1
Group IV (30 - 0)	0	0.0
Total	52	100.0
$\bar{X}$ ± SD	68.5 ± 14.7	

All studied patients were tested for mutations in IDH, TP53 genes and determined MGMT promoter methylation status. The results in table 2 showed that for IDH gene mutations, grade III patients had a positive rate higher than grade IV; and for P53 gene mutation, the positive rate in grade IV patients is higher than in grade III patients. While the rate of MGMT promoter methylation in the 2 groups of patients was almost similar.

Table 2 - IDH, TP53 gene mutation and MGMT promoter methylation status in the studied patients

WHO grade	IDH mutation		P53 mutation		MGMT methylation	
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
III	12 (23.1)	6 (11.5)	10 (19.2)	8 (15.4)	9 (17.3)	9 (17.3)
IV	6 (11.5)	28 (53.8)	15 (28.8)	19 (36.5)	13 (25.0)	21 (40.4)
Total	18 (34.6)	34 (65.4)	25 (48.1)	27 (51.9)	22 (42.3)	30 (57.7)

WHO: World Health Organization

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Relationship between patient characteristics and the presence or absence of different types of mutations

Research results in table 3 show that there is a statistically significant relationship between pathology results, malignancy and IDH mutation status in the studied patients; no relationship was found between IDH mutation status and characteristics of age, sex, Karnofsky score at hospital admission (all p-values > 0.05).

Table 3 - The relationship between some clinical and laboratory features and the presence or absence of IDH mutations

Features		IDH mutations		p – value
		Yes n (%)	No n (%)	
Age groups	< 50	13 (72.2)	18 (52.9)	0.239
	≥ 50	5 (27.8)	16 (47.1)	
Sex	Male	10 (55.6)	22 (64.7)	0.561
	Female	8 (44.4)	12 (35.3)	
Pathology	Anaplastic astrocytoma	4 (22.2)	5 (14.7)	< 0.001
	Anaplastic oligodendroglioma	8 (44.4)	1 (2.9)	
	Glioblastoma	6 (33.3)	28 (82.4)	
Grade of maglinancy	III	12 (66.7)	6 (17.6)	0.001
	IV	6 (33.3)	28 (82.4)	
Karnofsky score on admission	≥ 80	10 (55.6)	20 (58.8)	1.00
	< 80	8 (44.4)	14 (41.2)	

In this study, there was no statistically significant relationship between the characteristics of age, sex, histopathological results, malignancy and Karnofsky score at hospital admission of study patients (all p-values > 0.05) (table 4).


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Table 4 - The relationship between some clinical and laboratory features with the presence or absence of p53 mutations

Features		p53 mutations		p – value
		Yes n (%)	No n (%)	
Age groups	< 50	17 (68.0)	14 (51.9)	0.270
	≥ 50	8 (32.0)	13 (48.1)	
Sex	Male	15 (60.0)	17 (63.0)	1.00
	Female	10 (40.0)	10 (37.0)	
Pathology	Anaplastic astrocytoma	7 (28.0)	2 (7.4)	0.130
	Anaplastic oligodendroglioma	3 (12.0)	6 (22.2)	
	Glioblastoma	15 (60.0)	19 (70.4)	
Grade of maglinancy	III	10 (40.0)	8 (29.6)	0.562
	IV	15 (60.0)	19 (70.4)	
Karnofsky score on admission	≥ 80	14 (56.0)	16 (59.3)	1.00
	< 80	11 (44.0)	11 (40.7)	

Relationship between RECIST responding and the presence or absence of different types of mutations

Patients with the mutant expression of the IDH gene, p53, with MGMT methylation status had better RECIST responses than patients without these expressions. There is a relationship between IDH, p53 gene mutation status and MGMT methylation status of the study group with objective response according to RECIST (p-values < 0.05) (table 5).

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Table 5 - The relationship between the objective response according to the RECIST classification and the presence or absence of IDH mutations

RECIST responding	IDH mutations		p53 mutations		Methylation of MGMT		Total
	Yes	No	Yes	No	Yes	No	
Fully reposnsive	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	2 (3.8)
Partial reposnsive	4 (80.0)	1 (20.0)	5 (100.0)	0 (0.0)	4 (80.0)	1 (20.0)	5 (9.6)
Stable disease	12 (27.3)	32 (72.7)	18 (40.9)	26 (59.1)	16 (36.4)	28 (63.6)	44 (84.6)
Progressive disease	0 (0.0)	1 (1.00)	0 (0.0)	1 (100.0)	0 (0.0)	1 (1.00)	1 (1.9)
Total	18 (34.6)	34 (65.4)	25 (48.1)	27 (51.9)	22 (42.3)	30 (57.7)	52 (100)
p – value	0.007		0.004		0.041		-

DISCUSSION

The average age of the study sample was 45.2 ± 14.4 years old, in which the most common age group was from 40 to 49 years old, accounting for 26.9 % and the lowest age was 7 years old, the highest was 70. This result is also consistent with many other studies; *Ramussen's BK* et al[6] study showed that in patients with high-grade glioma, the age of the disease often appeared over 50 years of age.[6] Other studies[7] have shown that the median age of high-grade astrocytomas is usually over 40 years of age. At the same time, there were more men than women in this study with the corresponding rate of 62.7 % compared with 37.3 % (ratio of 1.6:1.0).

The results of domestic and international studies show that, although the male/female ratio varies between studies, these ratios show that in high-grade glioma, the male ratio is higher than women.[3,8] The Karnofsky score shows the patient's ability to live and work; in the present study, the Karnofsky score of the study subjects upon admission was mainly in group I (42.3 %) and group II (34.6 %). Only 12 patients (23.1 %) belonged to group III. The mean Karnofsky score of the patients was 68.5 ± 14.7. Patients who come to the hospital with a good general condition (Karnofsky score: 90-100) will have better treatment outcomes than patients who come with a poor general condition. Patients who come to the hospital with severe systemic conditions are often found having large tumors causing compression and invasion of functional areas around the tumor; at this time surgery to remove the

maximum of tumor is very limited due to avoiding complications during surgery as well as serious sequelae.

In this study, all patients were tested for IDH gene mutations (IDH1 and IDH2), P53, determined the MGMT methylation status, and the relationship between these mutations and the response to therapy. According to RECIST values, the presence of these gene mutations has a positive effect on the level of objective response RECIST.

Research results show that for IDH gene mutation, grade III patients have a higher positive rate than grade IV. The outcomes of this study are consistent with other studies showing that mutations in the IDH gene were high in grade III gliomas, while rare in glioblastomas (grade IV).[9,10,11] Another study found that IDH1 mutations have a high prevalence in low-grade gliomas (grade II gliomas and secondary gliomas), such as diffuse astrocytomas (68 %), oligodendroglioma (69 %) and secondary glioblastoma (88 %); the finding that IDH1 mutation is an early marker in the development of glioma.[12] It is believed that mutations in the IDH1 gene are present in the late stages of the tumor and the early stages of the disease. Therefore, IDH1 mutations may be tumorigenic and play an essential role in the development of gliomas. The presence of mutations in the IDH gene group affects treatment decisions and the prognosis of post-treatment response. A large study by *Cairncross JG* et al[13] showed that the median survival of the group of patients with IDH gene mutations treated with chemotherapy and radiotherapy was significantly higher than that of patients with radiotherapy alone (9.4 years vs. 5.7 years). In contrast to the group without the IDH gene mutation, there was no difference between the two treatment options (1.3 and 1.8 years).

For P53 gene mutation, the present study showed that 55.6 % (10/18) and 44.1 % (15/34) were positive in grade III and IV glioma; similar results to those of *Tada M* et al[14] when the mutation rate was 67 % in non-proliferative astrocytomas (WHO grade III) and 41 % in glioblastomas (GBM, WHO grade IV). In GBM, mutant TP53 was mainly found in secondary GBM, accounting for about 67 % of glioblastomas, whereas mutation frequency in primary GBM was lower (11 %). In contrast to carcinomas in which TP53 gene mutations occur late in tumor progression, but in astrocytomas with TP53 mutations appear early.[15]

TP53 mutations occur at nearly the same frequencies in astrocytomas showing the progression from


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WHO grade II to IV. The TP53 mutation is a genetic marker of secondary GBM because these tumors have a mutation rate in this gene (> 65), suggesting that the p53 pathway plays an important role in development of tumors.[16,17,18,19] When analyzing the association between TP53 mutations and treatments, recent studies have shown that the status of the TP53 gene affects the effectiveness of DNA alkylation treatment by using temozolomide (TMZ) - the most effective chemotherapeutic agent for GBM. *Blough MD* et al[20] showed that GBM cell lines that do not express functional p53 are significantly more sensitive to TMZ than cell lines that express functionally intact wild-type p53, altered p53 expression or function had only a small effect on TMZ sensitivity in the initiation of cytoskeletal brain tumors and tended to decrease sensitivity to TMZ.

The MGMT promoter methylation status occurred in the study group with a rate of over 42.3 %. The results of this study are similar to the study of *Weller M* et al,[21] showing that in high-grade gliomas, the promoter methylation rate of the MGMT gene is about 40 % in primary GBM and 70 % in secondary GBM; this methylation is also seen in 1/2 diffuse astrocytoma, as well as in two-thirds of oligodendrogliomas and mixed gliomas.[21] Many studies have demonstrated that MGMT promoter methylation status improves survival in patients treated with temozolomide-containing regimens.[22] Because of its role in predicting treatment response to TMZ, MGMT promoter methylation status has been routinely used in most treatment recommendations[23,24] and to guide future clinical trials.

Through a study on 52 patients who met the selection criteria for the study, we found that the IDH gene mutation showed that patients with grade III glioma had a higher positive rate than grade IV; P53 gene mutation occurred mainly in patients with grade IV glioma; MGMT methylation occurred in 42.3 % of the studied patients. There is a relationship between IDH gene mutation with pathological results and malignancy in studied patients. At the same time, the presence of mutations in IDH, P53 genes, and MGMT methylation status has been shown to be a beneficial factor for treatment response as assessed by RECIST.


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Conflict of interest

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Authorship contribution

Conceptualization: *Tran Anh Duc, Nguyen Duc Lien.*

Data curation: *Tran Anh Duc, Nguyen Thanh Bac.*

Formal analysis: *Tran Anh Duc.*

Research: *Tran Anh Duc, Nguyen Van Ba, Vu Van Hoe, Nguyen Thanh Bac, Nguyen Duc Lien.*

Methodology: *Tran Anh Duc, Nguyen Duc Lien.*

Supervision: *Nguyen Duc Lien, Nguyen Van Ba, Vu Van Hoe.*

Validation: *Nguyen Thanh Bac, Vu Van Hoe.*

Display: *Tran Anh Duc, Nguyen Duc Lien.*

Drafting - original draft: *Tran Anh Duc, Nguyen Duc Lien, Nguyen Van Ba, Nguyen Thanh Bac.*

Drafting - revision and editing: *Tran Anh Duc, Nguyen Duc Lien, Nguyen Van Ba, Nguyen Thanh Bac.*