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Meningiomas and the tumor microenvironment: expression of PD-L1 and expression of PD-L1 and interferon-gamma in the prognosis

Meningiomas e microambiente tumoral: expressão de PD-L1 e interferon gama no prognóstico

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ABSTRACT

Introduction: Meningiomas are the most common intracranial tumors in adults. One of the mechanisms used by tumor cells to escape death by immune cells is to interfere with immunological checkpoints, thereby preventing the establishment of adequate immune response. Following this concept, a promising target for an immunomodulatory therapy is blocking programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1 axis), which is known to be crucial for immune escape mechanisms. Interferon-gamma (IFN-γ) is related to PD-L1 expression, produced by activated T cells, and may promote hyper-regulation of PD-L1 expression in tumor cells. **Methods:** The retrospective cross-sectional cohort study analyzed 93 patients diagnosed with meningioma of different degrees, and immunohistochemical reactions of PD-L1 and IFN-γ proteins were performed. **Results:** This study did not detect PD-L1 immunoexpression in any of the 93 analyzed cases. The PD-L1 expression in meningioma cells and their potential role in local immunosuppression are not fully established and their indication for anti-PD-L1 therapy as an alternative treatment for meningiomas is still controversial. **Conclusion:** IFN-γ immunoexpression was related to lower rates of tumor recurrence and longer progression-free survival time; there was also a relationship with the absence of pleomorphism, better differentiation and lower tumor grade for this marker.

Key words: meningioma; tumor microenvironment; prognosis.

RESUMO

Introdução: *Os meningiomas são os tumores intracranianos mais comuns em adultos. Um dos mecanismos utilizados por células tumorais para escapar da morte por células imunes é interferir em* checkpoints *imunológicos, impedindo, assim, o estabelecimento de resposta imune adequada. Seguindo esse conceito, um alvo promissor para uma terapia imunomoduladora é o bloqueio do eixo de morte celular programada 1 (PD-1)/ligante de morte celular programada 1 (PD-L1), conhecido por ser crucial para mecanismos de escape imune. O interferon gama (IFN-γ) se relaciona com a expressão de PD-L1, sendo produzido por células T ativadas; pode promover a hiper-regulação da expressão de PD-L1 em células tumorais.* ***Métodos:*** *Estudo de coorte transversal retrospectivo que analisou 93 pacientes diagnosticados com meningioma de diversos graus. Reações imuno-histoquímicas das proteínas PD-L1 e do IFN-γ foram realizadas.* ***Resultados:*** *Este estudo não detectou imunoexpressão de PD-L1 em nenhum dos 93 casos analisados. A expressão de PD-L1 em células de meningioma e seu papel potencial na imunossupressão local não estão totalmente estabelecidos, e a indicação de terapia anti-PD-L1 como tratamento alternativo para meningiomas ainda é controversa.* ***Conclusão:*** *A imunoexpressão de IFN-γ relacionou-se com menores taxas de recidiva tumoral e maior tempo de sobrevida livre de progressão de doença. Constatou-se ainda relação com ausência de pleomorfismo, melhor diferenciação e menor grau tumoral para este marcador.*

Unitermos: *meningioma; microambiente tumoral; prognóstico.*

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RESUMEN

Introducción: *Los meningiomas son los tumores intracraneales más comunes en personas adultas. Uno de los mecanismos utilizados por células tumorales para escapar de la muerte es interferir con los puntos de control inmunológicos, impidiendo así el establecimiento de una respuesta inmunitaria adecuada. Siguiendo este concepto, un objetivo prometedor para una terapia inmunomoduladora es el bloqueo del eje de la proteína de muerte celular programada 1 (PD-1)/ligando 1 de muerte celular programada (PD-L1), que es conocido por ser crucial para los mecanismos de escape inmune. El interferón gamma (IFN-γ) se relaciona con la expresión de PD-L1, es producido por células T activadas y puede promover la hiperregulación de la expresión de PD-L1 en células tumorales.* ***Métodos:*** *El estudio de cohorte transversal retrospectivo analizó a 93 pacientes diagnosticados con meningioma de grados variables; se realizaron reacciones inmunohistoquímicas de las proteínas PD-L1 y del IFN-γ.* ***Resultados:*** *Este estudio no detectó inmunoexpresión de PD-L1 en ningún de los 93 casos analizados. La expresión de PD-L1 en células de meningioma y su función potencial en la inmunosupresión local no están totalmente establecidas, y su indicación de terapia anti-PD-L1 como tratamiento alternativo para meningiomas aún es controvertida.* ***Conclusión:*** *La inmunoexpresión de IFN-γ se relacionó con bajas tasas de recidiva tumoral y más tiempo de supervivencia libre de enfermedad, y se constató relación con ausencia de pleomorfismo, mejor diferenciación y grado tumoral más bajo para este marcador.*

Palabras clave: *meningioma; microambiente tumoral; pronóstico.*

INTRODUCTION

Meningiomas originate from arachnoid cells of the meninges and are the most common intracranial tumors in adults[1-4]. They represent approximately 35% of primary tumors of the central nervous system (CNS), with an incidence of 7.44 cases per 100,000 inhabitants in the United States[5]. Meningiomas can develop in patients at any age, although they are more common between 60 and 70 years[5, 6]. Women are three times more likely to develop meningiomas than men[6]. Most meningiomas are benign tumors that grow slowly, with a low recurrence rate and long survival time[7]; most tend to be localized, and non-invasive. However, some meningiomas behave aggressively, with invasion of the adjacent brain, high propensity to recurrence and, in rare cases, extracranial metastases[8].

Interactions between immune and neoplastic cells play an important role during malignant progression that has been designated as the concept of cancer immunodeficiency[9]. One of the mechanisms used by tumor cells to escape death by immune cells is to interfere in immunological checkpoints, thus preventing the establishment of an adequate immune response[10]. Following this concept, a promising target for an immunomodulatory therapy is the programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis, which is known to be crucial for immune escape mechanisms[11, 12].

Interferon-gamma (IFN-γ) is related to the PD-L1 expression, it is produced by activated T cells and can promote the hyper-regulation of PD-L1 expression in tumor cells by molecular mechanisms that have not yet been fully elucidated[13]. This effect is called "adaptive immune resistance"[13]. Some studies present interferon therapy as an alternative for the treatment of refractory and recurrent meningiomas[14-16]. Evidence suggests its antiproliferative, immunomodulatory and antiangiogenic activity on these tumors[15, 16].

OBJECTIVES

To evaluate the expression of the PD-L1 and IFN-γ immune modulator and its relationship with progression-free survival, as well as to analyze the correlation between clinical and morphological aspects with the immunoexpression of PD-L1 and IFN-γ: age, sex, location, tumor grade, invasion of cerebral parenchyma, presence of macronucleoli, spontaneous necrosis, hypercellularity, morphological subtypes, tumor pleomorphism, mitotic activity.

METHODS

The study was a retrospective cross-sectional cohort, which analyzed 93 patients diagnosed with meningioma from a database and files from a private laboratory for surgical pathology in the city of Fortaleza, Ceará, Brazil, from 2010 to 2018. All pathological diagnoses were reviewed and confirmed by two neuropathologists according to the criteria of the World Health Organization (WHO) in its last edition of 2016. The clinical parameters analyzed were: age, sex, tumor location, and progression-free survival during the

study period. Disease progression-free survival was defined as time from the patients' initial diagnosis to the date of tumor recurrence detection or completion of the study follow-up period in 2018. Tumor recurrence after initial treatment or patient death due to disease complication, during the study period, was considered as disease progression. The pathological parameters analyzed were tumor grade, mitotic index, cerebral parenchyma invasion, presence of macronucleoli, spontaneous necrosis, hypercellularity, and pleomorphism. Two paraffin blocks containing samples of all tumors were prepared using the tissue micro-array (TMA) technique. Punches of 2 mm were performed in previously established areas of the tumors in paraffin blocks selected from each case. In total, 93 punches were performed, and two blocks of TMA were prepared.

The immunohistochemical reaction of the PD-L1 protein was performed using two clones: 1. Ventana SP263 clone (Roche Diagnostics, 740-4907); 2. Dako 22C3 clone (DAKO Autostainer, AS480). To interpret the results, only the PD-L1 expression in tumor cells was evaluated, considering that these tumors do not usually present tumor infiltrating lymphocytes in their microenvironment. PD-L1 positivity was defined by the positive percentage of any membrane staining intensity. PD-L1 expression was grouped into positive and negative cases. The IFN-γ immunohistochemical reaction was performed using clone 4SB3 (Ventana Medical Systems, Inc., Tucson-AZ). The intracellular tumor marking of any intensity was considered as positive, and the absence of tumor marking, as negative. The IFN-γ expression was grouped into positive and negative cases.

The patients were selected from a database and file from a private laboratory of surgical pathology in the city of Fortaleza, Ceará, Brazil, who were diagnosed with meningioma of any degree or morphological subtype and who presented clinical information properly reported on application forms for anatomopathological study, in addition to the possibility of contact to obtain information on recurrence, complications and death related to the disease. Patients who did not have sufficient tumor tissue for immunohistochemical analysis, presented inadequate records of clinical information, those who did not receive standard treatment with surgery and/or radiotherapy, or were unable to contact to obtain new information were excluded.

The data were tabulated in the Microsoft Excel and exported to the Statistical Package for the Social Sciences (SPSS) software version 20.0 for Windows, in which the analyzes were performed with a 95% confidence interval. The absolute and percentage frequencies of each variable were expressed, which were crossed using Fisher's exact test or Pearson's chi-square test.

RESULTS

There was no PD-L1 immunoexpression in any of the 93 cases analyzed, evaluating the two clones used. Immunohistochemical reactions were validated with positive external controls and specific protocols followed for each antibody tested (**Figure 1**).

From the total number of patients evaluated, 22.6% presented IFN-γ immunoexpression (**Figure 2**). It was observed that women had a higher IFN-γ expression than men, 52.4% (p = 0.03) (**Table 1**).

Our study showed that most tumors with IFN-γ immunoexpression, were located in brain lobes, 42.3%, when compared with other topographies (p = 0.014) (Table 1).

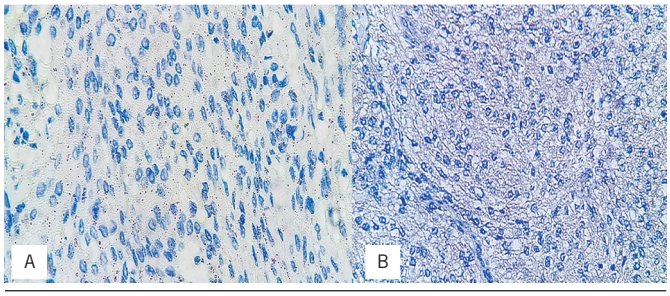

FIGURE 1 – *Negative immunohistochemical reactions with the two tested clones (20× magnification). Absence of complete circumferential or partial membrane staining in all evaluated cases*

Source: prepared by the author.

A) PD-L1: clone 22C3 Dako; B) PD-L1: SP263 Ventania.
PD-L1: programmed cell death ligand 1.

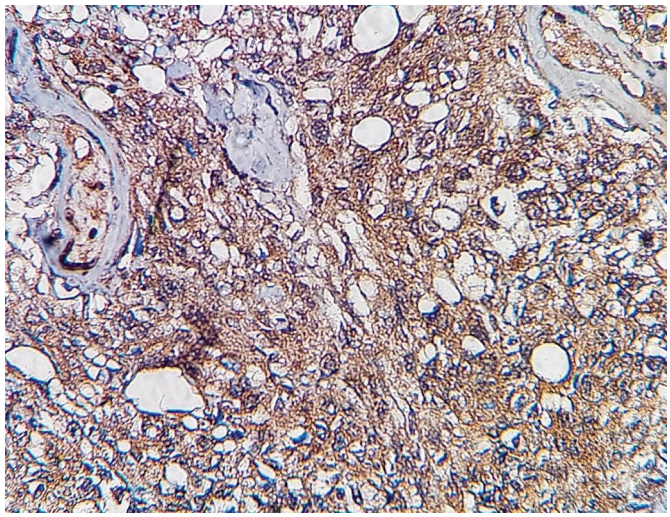

FIGURE 2 – *Immunohistochemical reaction for IFN-γ (20× magnification); diffuse positivity in lesion cells*

Source: prepared by the author.

IFN-γ: interferon-gamma.

TABLE 1 – Analysis of IFN-γ immunoexpression and its relationship with the clinical variables in patients with meningioma

	IFN-γ				
	No		Yes		*p* value
	n	%	*n*	%	
Age					
Up to 55	37	51.4	10	47.6	0.761
> 55	35	48.6	11	52.4	
Sex					
Female	55*	76.4	11	52.4	0.033
Male	17	23.6	10*	47.6	
Site					
Brain lobes	40*	55.5	9	42.3	0.014
Meninges	5	6.9	0	0	
Sphenoid	4	5.6	0	0	
Extra-axial	2	2.8	5*	23.8	
Extradural	3	4.2	0	0	
Olfactory bulb/gutter	5*	6.9	0	0	
Other	13	18.1	7*	33.9	

Source: prepared by the author.
*IFN-γ: interferon-gamma; *p < 0.05, Fisher's exact test or Pearson's chi-square.*

IFN-γ immunoexpression was also related to the absence of pleomorphism in tumor cells, revealing that this marker confers better differentiation and less tumor grade. From the total patients with IFN-γ immunoexpression, 85.7% did not exhibit cellular pleomorphism and 14.3% exhibited only mild pleomorphism. None of the tumors with moderate or severe pleomorphism showed IFN-γ immunoexpression ($p = 0.04$) (**Table 2**).

From the total patients who presented IFN-γ immunoexpression, 71.4% were grade I meningiomas, 28.6% were atypical meningiomas. None of the grade III tumors showed IFN-γ immunoexpression ($p = 0.13$). From grade I tumors, the meningothelial and fibrous subtypes were the ones that most expressed IFN-γ with 33% and 19%, respectively ($p = 0.5$) (Table 2 and **Figure 3**).

The IFN-γ immunoexpression was presented as a variable that reduces the risk of recurrence and improve progression-free survival. From the total of cases that recurred, about 85%, did not exhibit IFN-γ immunoexpression ($p = 0.36$) (**Table 3**). It is also noteworthy that in this study, the cases that presented IFN-γ expression had an average of 71 months of progression-free survival, against 65 months of the cases that did not present immunoexpression of this marker ($p = 0.228$). These results, however, did not show statistical significance.

When we consider IFN-γ immunoexpression as a forcing input variable, it is, therefore, the variable that, even though it does not significantly influence the outcome of progression-free survival, is the focus of the study, we find that the absence of the

TABLE 2 – Analysis of IFN-γ immunoexpression and its relationship with morphological variables in patients with meningioma

	IFN-γ				*p* value
	No		Yes		
	n	%	*n*	%	
Mitotic index					
0 cells	58	80.6	14	66.7	0.18
> 0 cells	14	19.4	7	33.3	
Invasion of the cerebral parenchyma					
No	68	94.4	20	95.2	0.887
Yes	4	5.6	1	4.8	
Macronucleus					
No	67	93.1	19	90.5	0.693
Yes	5	6.9	2	9.5	
Necrosis					
No	64	88.9	16	76.2	0.14
Yes	8	11.1	5	23.8	
Hypercellularity					
No	71	98.6	21	100	0.587
Yes	1	1.4	0	0	
Pleomorphism					
Absent	65	90.3	18	85.7	0.044
Mild	1	1.4	3	14.3	
Moderate	5	6.9	0	0	
Intense	1	1.4	0	0	
Morphological subtype					
Anaplastic	3	4.2	0	0	0.571
Angiomatous	1	1.4	1	4.8	
Atypical	9	12.5	6	28.6	
Fibrous	9	12.5	4	19	
Meningothelial	37	51.4	7	33.3	
Metaplastic	2	2.8	1	4.8	
Papillary	1	1.4	0	0	
Psammatous	5	6.9	1	4.8	
Transitional	5	6.9	1	4.8	
Histological grade					
I	59	81.9	15	71.4	0.136
II	9	12.5	6	28.6	
III	4	5.6	0	0	
Histological grade					
I	59	81.9	15	71.4	0.293
II/III	13	18.1	6	28.6	

Source: prepared by the author.
*IFN-γ: interferon-gamma; *p < 0.05, Fisher's exact test or Pearson's chi-square.*

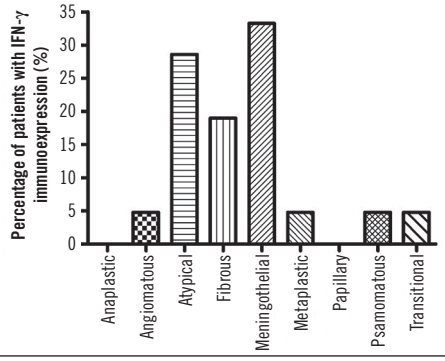

FIGURE 3 – *IFN-γ immunoexpression in the morphological subtypes of meningiomas*
Source: prepared by the author.
IFN-γ: interferon-gamma.

TABLE 3 – Analysis of IFN-γ immunoexpression and its relationship with the rate of tumor recurrence in patients with meningioma

			Recurrence				
	Total		No		Yes		*p* value
IFN-γ	*n*	%	*n*	%	*n*	%	
No	72	77.4	55	75.3	17	85	0.360
Yes	21	22.6	18	24.7	3	15	

Source: prepared by the author.
*IFN-γ: interferon-gamma; *p < 0.05, Fisher's exact test or Pearson's chi-square.*

expression of this marker relates with a 3.46-fold reduction in the mean time to progression-free survival ($p = 0.01$) (**Figure 4** and **Table 4**).

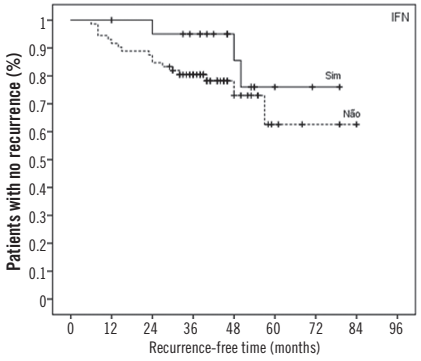

FIGURE 4 – *Kaplan-Meier curve relating the recurrence-free time and the percentage of patients without tumor recurrence*

Source: prepared by the author.

TABLE 4 – Multivariate analysis of clinical and morphological variables, using IFN as a forcing input variable

	p value	HR	CI 95%	
Disease progression-free time				
Sex (male)	0.623	1.37	0.39	4.73
Mitotic index (> 0)	0.482	1.96	0.3	12.75
Invasion of the cerebral parenchyma (Yes)	0.595	1.48	0.35	6.23
Macronucleus (Yes)	0.383	0.43	0.06	2.86
Necrosis (Yes)	0.692	1.3	0.35	4.79
Hypercellularity (Yes)	0.375	3	0.27	33.94
Pleomorphism (present)	0.358	2.26	0.4	12.89
Morphological subtype (anaplastic/atypical)	0.474	3.26	0.13	82.87
Histological grade (II/III)	0.306	7.79	0.15	396.31
Disease progression-free time (IFN as a forcing input variable)				
Sex (male)	0.392	1.52	0.58	3.94
Mitotic index (> 0)	0.623	1.49	0.3	7.31
Invasion of the cerebral parenchyma (Yes)	0.965	0.98	0.33	2.89
Macronucleus (Yes)	0.478	0.63	0.18	2.23
Necrosis (Yes)	0.288	1.71	0.64	4.56
Hypercellularity (Yes)	0.42	2	0.37	10.78
Pleomorphism (present)	0.353	1.73	0.54	5.51
Morphological subtype (anaplastic/atypical)	0.482	2.19	0.25	19.47
Histological grade (II/III)	0.127	8.33	0.55	126.77
IFN (absent)	0.012	3.46	1.31	9.15

Source: prepared by the author.
*IFN: interferon; HR: hazard risk; CI: confidence interval; *p < 0.05, COX regression.*

DISCUSSION

Some studies have shown that PD-L1 was found to be highly expressed in glioblastoma[17, 18], as well as in high-grade meningiomas[19], increasing the possibility of inhibition of the immune checkpoint in central nervous system tumors for which clinical trials are in progress[19, 20]. Immunohistochemistry studies evaluated the PD-L1 expression in tumor cells and concluded that the greater PD-L1 expression in the tumor and in the tumor microenvironment correlates with a worse prognosis and reduced survival time and/or a higher tumor grade[21, 22]. Some recent clinical trials of agents targeting PD-1 or PD-L1 have demonstrated durable tumor regression and prolonged disease stabilization in patients with non-small cell lung cancer, melanoma, clear cell renal cell carcinoma, and Hodgkin's lymphoma[23-27].

Our study did not detect PD-L1 immunoexpression in any of the 93 cases analyzed.

Wang *et al*. (2018)[28] studied the PD-L1 immunoexpression in tumors related to neurofibromatosis type 1 and 2, analyzing a total of 10 meningiomas of unspecified grade in patients with neurofibromatosis type 2. This study worked with TMA blocks and performed immunohistochemical reactions with two clones of anti-PD-L1 antibodies (SP142 and E1L3N clones), considered as positive the cases that presented more than 5% of PD-L1 membrane expression in tumor cells. The results showed PD-L1 immunoexpression in four out of 10 cases for SP142 clone and two of cases for E1L3N clone. These divergences in relation to our study seem to be associated with the difference in clones used and the fact that the sampling of selected meningiomas are all related to patients with neurofibromatosis and have significant populations of tumor infiltrating lymphocytes, which were also accounted for in this work[28].

On the other hand, Du *et al*. (2014)[29] found high expression of the PD-L1 protein in about 40% grade I, 60% grade II, and 80 grade III. This study detected the presence of messenger ribonucleic acid (mRNA) related to PD-L1 by the of reverse transcription polymerase chain reaction (RT-PCR) technique, with ribonucleic acid (RNA) extraction from a frozen sample of meningiomas of various degrees, in addition to research into the immunoexpression of the PD-L1 protein by the Immunoblot technique. These differences in the PD-L1 immunoexpression found may reflect the need to use more accurate molecular techniques that reflect the real expression of this protein.

We also point out that the fact that our study used the technique of material representation by TMA, in which some representative areas of the tumor are selected to perform immunohistochemical

reactions, there may be sampling bias in the analysis of the tumors, considering that only one area will be subjected to analysis and not the entire tumor extension.

A recently published report showed the case of a patient with metastatic pulmonary adenocarcinoma who was also diagnosed with meningioma, he was treated with the anti-PD-L1 monoclonal antibody Nivolumabe, for the former. There was a decrease in the size of the meningioma[30].

The treatment of meningiomas with the monoclonal anti-PD-L1 antibody showed a significant decrease in tumor size according to Gelerstein *et al*. (2017)[30]. PD-L1 was also found expressed in infiltrating macrophages in meningiomas, in addition to tumor cells[31,32]. This may indicate that the populations of immune cells in the tumor microenvironment interfere with the immunoexpression of PD-L1.

In a recent study, Hao S *et al*. (2019)[33] evaluated 92 cases of skull base meningiomas, performing gene sequencing to check for mutations that could be associated with immunological checkpoint inhibition pathways. They concluded that meningiomas that showed the TRAF7 mutation had higher levels of PD-L1 expression, which was measured by immunohistochemistry and Western blot techniques, further affirming the crucial role of mutagenic pathways in suppressing the immune response in the tumor microenvironment. This study provides us with a reflection on the role of several mutagenic pathways that are related to tumor immune escape mechanisms and that influence the PD-L1 expression and that are not yet fully elucidated.

However, other previous studies have shown results similar to ours[28,34], revealing low PD-L1 expression, even suggesting that the expression of this biomarker is uncommon in meningiomas.

Some authors even question the applicability of immunotherapy in meningiomas and argue that this treatment becomes an exceptional option in recurrent meningiomas cases that have a rich inflammatory T-cell infiltrate[35,36].

The PD-L1 expression in meningioma cells and its potential role in local immunosuppression are not fully established and its indication as an alternative treatment for meningiomas is still controversial[30-32].

IFN-alpha (IFN-α) treatment has been found to inhibit the growth of human meningioma cell lines cultured *in vitro*[15]. Studies also show that it is an alternative therapy for recurrent and refractory meningiomas. Evidence suggests its antiproliferative, immunomodulatory and antiangiogenic action on these tumors[37,38].

In a clinical trial conducted with recurrent and refractory WHO grade 1 meningiomas which underwent surgery and radiation therapy, IFN-α treatment demonstrated progression-free survival at six and 12 months of 52% and 29%, respectively[39].

Current treatment of high-grade meningioma uses cytoreductive surgery with the intent of complete resection, often involving more than one surgery, as well as radiation therapy. Chamberlain and Glantz (2008)[39] studied the use of IFN-α in the treatment of high-grade meningiomas, but concluded that there was no impact on survival. The results of six patients with a non-resectable and recurrent condition who received IFN-α for five days a week showed that one patient presented less tumor reduction and four patients showed stable disease that lasted up to 14 months[39].

A larger and longer study with 12 patients reported that nine patients had stable disease after treatment with IFN-α, which lasted up to eight years[40]. A more recent study published with 35 patients with grade I meningioma, who received subcutaneous INF-γ daily[39], showed that ten patients presented mild toxicity, requiring a reduction on the drug dose of the, but, in general, the drug was safe. Twenty-five patients (74%) had stable disease with a median time to tumor progression of seven months and only nine patients (26%) had disease progression[39,41].

Our study showed interesting results in relation to IFN-γ immunoexpression, pointing out that it is a possible variable that reduces the risk of recurrence and improves disease-free survival.

It was observed that patients with IFN-γ immunoexpression had lower rates of tumor recurrence and longer progression-free survival time, although we did not find statistical significance in some results, which can be attributed to a matter of sampling and studied population.

Considering IFN-γ as a forcing input variable, we found that the absence of expression of this marker reduces the mean time to progression-free survival by 3.46 times.

There was also a difference in immunoexpression in relation to the patient's gender, women showed a higher IFN-γ expression than men. Our study showed that most tumors with IFN-γ immunoexpression were in brain lobes, 42.3%.

Our study also found that IFN-γ immunoexpression was related to the absence of pleomorphism in tumor cells, showing that the marker confers better differentiation and less tumor grade, in addition to higher disease-free survival rates (71 months versus 65 months of those which did not present marker immunoexpression) it was inversely related to recurrence rates (85% of recurrence cases that did not show IFN-γ immunoexpression).

CONCLUSION

The PD-L1 expression in meningioma cells and its potential role in local immunosuppression are not fully established and its indication for anti-PD-L1 therapy as an alternative treatment for meningiomas is still controversial. Our study did not show PD-L1 immunoexpression in the analyzed cases, agreeing with several publications that suggest the low expression of PD-L1 in these tumors, advising that the role of immunotherapy with anti-PD-L1 antibodies in meningiomas may not have applicability and favorable results.

Patients with IFN-γ immunoexpression showed lower rates of tumor recurrence, progression-free survival time. There was also a difference in immunoexpression in relation to the patient's gender, women showed a higher expression of IFN-γ than men, and a higher expression in meningiomas located in brain lobes. IFN-γ immunoexpression was also related to the absence of pleomorphism in tumor cells and a lower tumor grade. We conclude that this is a possible biomarker in meningiomas, considering several publications, reports and clinical trials that propose the use of interferon as a therapeutic alternative.

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