Original Article

Evaluating Interleukin-16 Expression in Patients with Grade-3 and Grade-4 Glial Cell Tumors and Healthy Individuals

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Abstract

Background: This study evaluated the change in IL-16 levels in patients with high-grade glial tumors undergoing radiotherapy (RT) and healthy individuals (control group). **Materials and Methods:** Serum IL-16 levels of 35 high-grade glioma patients receiving radiotherapy (RT) and 30 healthy individuals were compared. We compared the IL-16 levels before (RT0) and after the (RT1) and IL-16 levels were measured and the relationship of this change with other characteristics such as age, gender, weight, height, and blood test results. **Results:** The RT0-IL-16 level was approximately 15 pg/ml higher than the RT1 measurement in the patient group. The mean RT0-IL-16 levels in the patient group were approximately 10 pg/ml higher than the mean IL-16 levels in the control group. Likewise, at the RT1 time-point, the mean IL-16 levels for the patient group were approximately 5 pg/ml lower than the mean IL-16 for the control group. The mean RT0-RT1-IL-16 value tended to be higher in female patients than in male patients. **Conclusion:** The application of RT reduces the overall IL-16 levels, suggesting the efficacy of RT, as well as the role of IL-16 in tumorigenesis.

Keywords: *IL-16, malignant glioma, radiotherapy*

Introduction

Glioblastoma multiformes (GBM) are malignant tumors of the central nervous system (CNS) with the worst prognosis in adults and maximum tumor resection of such high-grade glial tumors is essential to ensure a good prognosis.[1] Malignant gliomas are classified as glioblastoma multiforme (Grade (G)-4), anaplastic astrocytoma (G-3), mixed anaplastic oligoastrocytoma (G-3), and anaplastic oligodendroglioma (G-3).

Despite the application of multimodal treatments, such as RT and temozolomide (TMZ)-based chemotherapy, the survival for high-grade glial tumors is only 1.5 years. Eventually, treatment methods, such as immunotherapy, were introduced.[2]

Microglial cells are differentiated macrophages of the CNS and act as the primary cellular barrier for protection against different stresses to the CNS. In human and rat gliomas, the functioning of microglial cells is through an innate and adaptive immune response. During the encounter with a neuropathological scenario, microglial cells can get activated and perform phagocytosis, antigen presentation, and lymphocyte activation. Although the inflammatory operations of these cells have been extensively investigated, their activity in malignant gliomas has not been fully appreciated. It is known that microglial cells exert an anti-tumor effect by activating immune system, or may cause tumor growth in gliomas by releasing various immunomodulatory cytokines.[3] Recent studies have shown that activated microglia are present in and around existing benign brain tumors, as well as in nascent tumor masses, especially in astrocytic gliomas.[4] However, the role of microglial cells in the progression of malignant brain tumors remains undetermined. A greater understanding of this association will help discover and develop

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therapeutic agents with superior efficacy against glial cell tumors.

The protein, interleukin-16 (IL-16), and its bioactivity originate from human peripheral blood cells.[5] It was first identified in 1982 as T-cell chemoattractant factors stimulated by mitogen or an antigen. The IL-16 gene is located on chromosome 15, which is responsible for its release from activated CD8+ T-lymphocytes known as chemoattractant factors. IL-16, as a cytokine, functions and manages opposite (contradictory) inflammatory states; i.e., IL-16 is released by activated monocytic cells as a pro-inflammatory cytokine (known as a lymphocyte chemoattractant factor). It also acts as a modulator of T cells and a natural soluble solution for CD4+, which plays a regulatory role in asthma and many autoimmune diseases.[6-10]

In pathological conditions, the release of IL-16 release causes an increase in intracellular Ca^{2+} and inositol triphosphate, as well as protein kinase-C (PKC) translocation. These processes trigger the release of other pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), IL-1β, IL-6, and IL-15, which are involved in tumorigenesis. Thus, IL-16 is not only involved in the inflammatory response to tumor growth but also in tumor formation.[10-12]

The IL-16 protein functions in cell growth, communication, and differentiation, as well as in the differentiation and development of the immune system.[13,14] In the CNS, it is released by a subset of microglial cells in the human brain and contributes to attracting CD4+ lymphocytes across the blood–brain barrier in pathological conditions. IL-16 has been reported to be released by inflammatory cells in non-malignant CNS pathologies,[15-18] as well as human glioma cells.[19,20]

Therefore, this study evaluated the change in IL-16 levels in patients with high-grade glial tumors undergoing RT and healthy individuals. We compared the IL-16 levels before and after the RT and the relationship of this change with other characteristics such as age, gender, weight, height, and blood test results.

Materials and Methods

Patients and control groups

Patients (n = 35) with high-grade glial tumors (G-3 and G-4) were included in this prospective study between January 2019 and December 2021. The study was conducted after obtaining Ethical Approval (Date 01 June 2018, Decision number: 78 / 16). For the control group, 30 healthy individuals with normal brain contrast-enhanced magnetic resonance imaging (CE-MRI), i.e.,, no clinically relevant radiological findings, without any history of brain surgery or RT and any other comorbidities, were selected. All participants provided voluntary consent for participating in the study.

Procedure

All included patients, who were operated on with a preliminary diagnosis of G-3 and G-4 tumor and the operative pathology was confirmed as G-3 or G-4 glial tumor, were subjected to RT. Serum samples were taken before RT (RT0) and immediately after cessation of RT (RT1), and IL-16 levels were measured. In the control group, serum was obtained after the initial CE-MRI.

Radiotherapy

Before RT was started, contrast-enhanced magnetic resonance imaging (CE-MRI) was performed in the patients who all underwent total surgical resection.

For patients with healed surgical wounds, curative RT was given as 46Gy in phase 1. The dose was taken to 60Gy in total with a booster in phase 2. The radiation treatment was delivered over a total of 30 days. All patients received curative dose RT using IMRT treatment method with conventional 2Gy per fraction per day. The treatment was delivered using Electa Versa HD Linear Accelerator Device with 6 MV photons flattening filter free (FFF). The second serum samples were taken one day after the last dose of RT.

They also received TMZ-therapy concomitantly. During RT, all patients were evaluated weekly for toxicity as per the Radiation Therapy Oncology Group and the European Cancer Research and Treatment Organisation criteria.[21]

Measurement of IL-16 levels

About 5 cc of venous blood samples was taken from the patients at RT0 and RT1 time points and collected into serum tubes. The collected samples were centrifuged at 3000 rpm for 20 minutes; serum was separated and aliquoted to avoid repeating the freeze–thaw process and stored at −20°C until the test time. Just before the test, an aliquot was taken and allowed to reach room temperature for 30 min. For testing the IL-16 levels, BioTek ELX405R Microplate Washer BioTek Instruments EL800 Microplate Reader (serial no: 209224) and Human IL-16 enzyme-linked immunosorbent assay (ELISA) Kit (SunRed, Shanghai, China; commercially available lot: 201708) were used. The serum levels were calculated as per the manufacturer's instructions and presented in picogram/milliliter (pg/ml).

Statistical analysis

All continuous variables were expressed descriptively using mean, standard deviation, and minimum and maximum values. Student's *t*-test was used to compare

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the IL-16 levels at RT0 and RT1. To determine the linear relation between IL-16 and other variables, Pearson's correlation coefficient was calculated. The statistical significance level was considered at a P value < 0.05. Statistical Package for Social Sciences (version 21.0, IBM Inc., Armonk, NY, USA) was used for all statistical computations.

Results

Of the 35 patients, 17 (48.57%) had G-3 tumors, while 18 patients had G-4 (51.42%) tumors. There were 15 (42.85%) female patients between the ages of 22–88 years and 20 (57.14%) male patients between the ages of 26–72 years. The mean weight of the patients was 68.63 kg (range: 49–94 kg), and the mean height was 165.47 cm (range:151–190 cm).

In the control group, there were 16 males (53.33%) and 14 females (46.66%), having a mean weight and height of 76.10 ± 12.45 kg and 165.47 ± 7.68 cm, respectively.

No toxicity was observed in any patients during the first, second, and third weeks of RT. However, in the fourth week, 16 patients (45.71%) had G-0 toxicity, 13 (37.14%) had G-1 Toxicity, and six (17.14%) had G-2 toxicity. In the fifth week of RT, G-0 toxicity was seen in 11 (31.42%) patients, G-1 in 15 (42.85%) patients, and G-2 in nine patients (25.71%). By the sixth week, three patients demonstrated toxicity (8.57%), 15 patients (42.85%) had G-1 toxicity, ten patients (28.57%) had G-2 toxicity, and seven (20%) had G-3 toxicity.

Results of the within-group comparison for the change in IL-16 values at RT0 and RT1 are presented in Table 1. The mean WBC count at RT0 was 9.291×10^3 cells as compared to 7.813×10^3 cells at RT1 ($P < 0.05$); i.e., a decrease of approximately 1.5 units was observed at RT1.

There were no statistically significant differences between RT0 and RT1 measurements in terms of

Table 1: Results of descriptive and statistical analysis of different variables in the patient group at RT0 (before initiating radiotherapy) and RT1 (immediately after the end of radiotherapy)

	Mean	Std. Dev.	Mean	Std. Dev.	p
RT0-IL-16	165.872	95.162	15.553	91.333	0.321
RT1-IL-16	150.319	50.003			
RT0-Neu	5.777	2.345	-0.379	3.760	0.555
RT1-Neu	6.155	4.314			
RT0-WBC	9.291	2.949	1.478	2.902	0.005
RT1-WBC	7.813	2.228			
RT0-HB	12.624	1.314	0.914	120.889	0.197
RT1-HB	13.032	1.676			
RT0-PLT	286.060	104.020	-0.409	1.809	0.965
RT1-PLT	285.140	73.554			
RT0-LYM	2.017	0.849	-0.298	1.066	0.107
RT1-LYM	2.315	0.957			
RT0-Ca	9.041	0.907	-0.100	0.952	0.545
RT1-Ca	9.141	0.550			
RT0-Na	138.917	3.952	1.360	5.714	0.168
RT1-Na	137.557	5.020			
RT0-K	4.428	0.612	0.159	0.808	0.252
RT1-K	4.269	0.561			
RT0-Cl	99.741	4.427	-0.031	6.312	0.978
RT1-Cl	99.772	4.906			
RT0-Fibrinogen	287.071	105.620	-21.265	151.162	0.425
RT1-Fibrinogen	308.336	103.937			
RT0-D-dimer	10.573	37.258	9.475	36.875	0.163
RT1-D-dimer	1.095	1.551			

Table 2: Results of correlation analysis between IL-16 and other variables in the patients

	RT0-IL-16	RT1-IL-16
Age	0.003	0.144
Weight	0.158	0.033
Height	0.232	0.041
RT0-Neu	0.120	-0.007
RT1-Neu	0.167	0.131
RT0-WBC	-0.107	-0.247
RT1-WBC	0.281	0.155
RT0-HB	-0.017	0.062
RT1-HB	-0.169	-0.039
RT0-PLT	-0.050	0.019
RT1-PLT	-0.110	-0.077
RT0-LYM	0.140	0.045
RT1-LYM	0.230	0.053
RT0-Ca	-0.079	0.412*
RT1-Ca	0.153	0.059
RT0-Na	0.251	-0.083
RT1-Na	0.412*	0.077
RT0-K	0.240	-0.295
RT1-K	0.205	0.127
RT0-Cl	-0.066	-0.113
RT1-Cl	0.247	0.243
RT0-Fibrinogen	-0.035	0.062
RT1-Fibrinogen	0.534**	0.232
RT0-D-dimer	-0.022	0.007
RT1-D-dimer	-0.178	-0.074

*: p < 0.05; **: p < 0.01

Table 3: Results of comparison between the patient and control groups

	Group	Mean	St. Dev.	Min.	Max.	p
IL-16	RT0 Patient	165.87	95.16	31.43	447.34	0.594
	Control	155.53	49.34	103.25	295.91	
IL-16	RT1 Patient	150.32	50.00	44.83	291.50	0.675
	Control	155.53	49.34	103.25	295.91	
IL-16 (RT0-RT1)	Patient	15.553	91.33	31.14	128.52	0.321

Table 4: Gender-based comparison of IL-16 levels in patients at the beginning (RT0) and immediately after the cessation (RT1) of radiotherapy

	Women				Men				p
	Mean	St. Dev.	Min.	Max.	Mean	St. Dev.	Min.	Max.	
RT0 IL-16	167.67	86.57	447.34	31.43	152.43	62.88	443.80	70.80	0.434
RT1 IL-16	157.84	61.07	295.91	44.83	145.97	26.92	218.53	101.59	0.341

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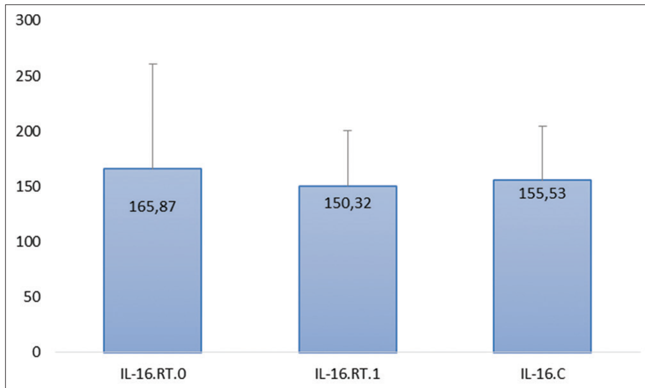

Figure 1: Change in Interleukin (IL)-16 levels in the patient and control groups

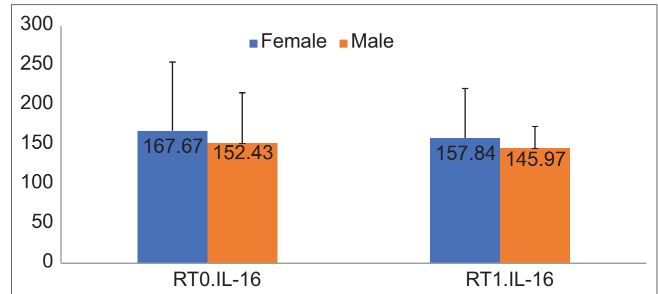

Figure 2: Gender-wise comparison of the change in interleukin (IL)-16 values before and after radiotherapy

other characteristics; notably, the RT0-IL-16 level was approximately 15 pg/ml higher than the RT1 measurement [Table 1].

Regarding the correlation analysis, there was no statistically significant correlation between IL-16 levels and other properties, except calcium (Ca), sodium (Na), and fibrinogen [Table 2]. A positive correlation (r = 0.41) was observed between RT0-Ca and RT1-IL-16 levels and RT1-Na and RT0-IL-16 levels; i.e., an increase in Ca and Na values tends to raise the IL-16 level by about 40.1%. Similarly, a positive correlation (r = 0.534) was observed between the RT1-fibrinogen and RT0-IL-16. Although statistically non-significant, a negative correlation was observed between RT0-IL-16 and RT1-IL-16 levels and RT0-WBC [Table 2].

The mean RT0-IL-16 levels in the patient group were approximately 10 pg/ml higher than the mean IL-16 levels in the control group. However, the difference was not statistically significant [Figure 1, Table 3].

Likewise, at the RT1 time-point, the mean IL-16 levels for the patient group were approximately 5 pg/ml lower than the mean IL-16 for the control group [Figure 1, Table 3].

This difference was not statistically non-significant. Although the difference (decrease) of 15 pg/ml in IL-16 levels between the RT0 and RT1 in the patient group was statistically non-significant, the overall IL-16 levels tended to decrease after RT [Figure 1, Table 3].

Lastly, a gender-wise comparison revealed no statistically significant difference between male and female patients in terms of the RT0-IL-16 value. However, the mean RT0-IL-16 value tended to be higher in female patients than in male patients [Figure 2, Table 4]. Similarly, although there was a gender-based statistically significant difference regarding the RT1-IL-16 value, the mean RT1-IL-16 levels were higher in female patients [Figure 2, Table 4].

Discussion

Physiologically, the immune system responds to cancer cells; however, in G-4 glial tumors, the exaggerated immune response mediated by IL-16 needs to be overcome.[2] IL-16 is a multifunctional cytokine, which is a critical pro-inflammatory factor with a crucial role in tumor development and tumor progression. In our study, there was a statistically significant difference between RT0-WBC and RT1-WBC levels in the patient group ($P < 0.05$), whereas the difference between RT0-IL-16 and RT1-IL-16 levels was not statistically significant [Table 1]. Nevertheless, the overall IL-16 cytokine level, measured using ELISA, decreased after RT. Furthermore, IL-16 levels were both positively and negatively affected by certain serum components [Table 2].

Previous studies have shown that IL-16 gene polymorphism is associated with the development of gastric cancer, colorectal cancer, and nasopharyngeal carcinoma.[22,23] IL-16 is known to be involved in the development of inflammatory diseases, as well as tumor formation and progression. Therefore, genetic mutations in the DNA sequence of the IL-16 gene may cause alterations in cytokine production and predispose the individual to the development of both colorectal cancer

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(CRC) and gastric cancer (GC). Gao *et al*.[22] investigated IL-16 levels in the sera of 60 CRC patients, 55 GC patients, and 61 controls using the ELISA method and reported that the mean IL-16 level was 7.09 ng/ml in CRC patients, 6.37 ng/ml in GC patients, and 3.23 ng/ml in the control group; i.e., the IL-16 levels were significantly higher than the control group ($P < 0.05$). Likewise, in our study, the mean value of RT0-IL-16 value for the patients was 10 pg/ml higher than the mean IL-16 in the control group. Notably, after RT (at RT1), the patient group had a lower mean value than the control group (difference: 5 pg/mL) [Table 3 Figure 1].

A combination of inflammatory cytokines acts in the development of cancer. Azimzadeh *et al*.[23] looked at three IL-16 gene polymorphisms (rs4072111, rs11556218, and rs4778889) in 260 CRC patients and 405 healthy controls. After isolating the genomic DNA from peripheral blood leukocytes of the patients and controls, IL-16 gene polymorphisms were examined using polymerase chain reaction (PCR), followed by the restriction fragment length polymorphism (RFLP) method. They found a significant association between the rs11556218-SNP gene polymorphism in IL-16 and CRC and stated that patients with rs11556218 gene polymorphism have a 1.75-fold risk of developing CRC ($P = 0.005$). They further described that the risk of developing CRC is low in male patients with rs4778889 gene polymorphism ($P = 0.045$). In our study, although statistically non-significant, we observed that the IL-16 values at both RT0 and RT1 tended to be higher in females than in males [Table 4, Figure 2].

Additionally, a possible association between IL-16 and nasopharyngeal carcinoma, prostate carcinoma, and glioma has been reported.[24-26] In a meta-analysis, Mo *et al*.[27] reported that the IL-16 gene rs11556218 T/G was specifically associated with nasopharyngeal carcinoma, CRC and the overall cancer risk. There were different cancers associated with IL-16, but IL-16 polymorphisms with cancer risk were found to be statistically more significant than in any single study. However, the change in IL-16 level was not associated with age, gender, body mass index, and alcohol and cigarette consumption in the patient and control.

Yu-Jin Tang *et al*.[28] analyzed the serum IL-16 levels in 82 osteosarcoma patients and 68 healthy individuals using ELISA. While the median plasma IL-16 value was 7.02 ng/mL (range: 0.48–56.87 ng/mL) in osteosarcoma patients, the control group had much lower values (median: 2.21 ng/mL, range: 0.09–50.48 ng/mL). The authors concluded that the IL-16 rs11556218 TG/GG genotypes may be associated with osteosarcoma, possibly by increasing the production of IL-16. This explains the role of IL-16 as a modulator protein, not only in the inflammatory process but also in tumorigenesis. These findings were further corroborated in our study; i.e., the mean value of RT0-IL-16 level of patients was approximately 10 pg/mL higher than the mean value for the control group.

Zhu *et al*.[29] measured IL-16 levels in the sera of 70 renal cell carcinoma (RCC) patients and 96 controls using the sandwich enzyme immunoassay method. The median IL-16 levels were 283.80 ± 80.66 pg/mL in patients and 409.80 ± 71.11 pg/mL in the control group ($P < 0.001$).

Moreover, the 295 T > C functional polymorphism in the promoter region of IL-16 was associated with the risk of developing RCC in the Chinese population; i.e., the 295 T > C polymorphism results in genetic predisposition to RCC. Likewise, Wu *et al*. found that the GG and TG genotypes of IL-16 rs11556218 were associated with an increased risk of lung cancer in the Taiwanese population irrespective of a smoking habit.[30]

Liebrich *et al*.[20] looked for IL-16 in brain tissue of healthy humans and patients with astrocytoma and reported that the patients had significantly increased IL-1 in parenchymal macrophages/microglia. They also observed that IL-16 increased in perivascular cells from G-2 astrocytoma tissue to G-3 astrocytoma tissue and this increase in IL-16 immunoreactivity was associated with G-3 and G-2 human glial tumors.[20]

Previous studies have also shown that IL-16 is excessively secreted in human and rat gliomas. Luo *et al*.[26] looked at IL-16 gene polymorphisms in 216 glioma patients and 275 control patients in China using the PCR-RFLP assay. An increased risk of glioma was observed in the IL-16 rs11556218TG genotype compared to the TT genotype. Similarly, an increased risk of glioma was observed in the rs11556218G allele compared to the T-allele. However, no significant association was observed between IL-16 rs4778889 and rs4072111 polymorphisms and the risk of glioma. These findings highlighted the possible role of IL-16 rs11556218 polymorphism as a susceptibility marker.

Inflammatory cytokines and cells play an important role in tumor development and chronic inflammation. While the pathology of many human malignant tumors is based on chronic inflammation, the exact mechanisms are unknown. Pro-inflammatory cytokine, IL-16, causes tumor growth and progression in patients with tumors since high IL-16 levels were found in patients with advanced-stage cancer and poor prognosis according to the tumor type. Accordingly, an association between IL-16 gene polymorphisms and cancer risk may be hypothesized.[27,31,32]

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Our study is a novel attempt to estimate the IL-16 levels using the ELISA method in patients with high-grade glial tumors receiving RT. In the RT0 period, the IL-16 level in the serum of all patients was found to be approximately 15 pg/ml higher than the RT1 IL-16 serum level.

IL-16 value decreased after RT. The mean value of IL-16 in the RT0 patient group was approximately 10 pg/ml higher than the mean value of IL-16 in the control group. However, the mean value of IL-16 in the RT1 patient group was approximately 5 pg/ml lower than the mean value of IL-16 in the control group. Additionally, the IL-16 value of the patient group after RT also decreased below the serum IL-16 value of the healthy people in the control group.

It was observed that the L-16 mean value measured at RT0 and RT1 times tended to be higher in female patients than in male patients.

Furthermore, according to the results of our study, the mean value of IL-16 was found to be higher in female patients than in male patients. After RT, it was observed that the mean value of IL-16 tended to decrease in all patients. Although the mean value of IL-16 before RT was higher than the mean value of IL-16 in the control group, the mean value of IL-16 after RT was found to be lower than the mean value of IL-16 in the control group. According to these results, IL-16 level decreases in the serum of patients receiving RT.

There were some limitations to our study. First, the age range is large (22-88 years). Second, the sample size of patients and control groups are relatively small in this study. Future studies with larger sample size are needed to clarify our findings.

Conclusion

The application of RT reduces the overall IL-16 levels, suggesting the efficacy of RT, as well as the role of IL-16 in tumorigenesis. Furthermore, we noted a correlation between RT and IL-16 values. These findings highlight the need to develop more effective immunotherapy treatments for these patients.

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Conflicts of interest

There are no conflicts of interest.

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