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Niacin Modulates Immune Responses in a Phase I Dose-Escalation Clinical Trial of Newly Diagnosed Glioblastoma

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Abstract

Background and Objectives

Glioblastoma, a highly aggressive and uniformly lethal brain tumor, resists current treatments and immunotherapies by creating a potently immunosuppressive microenvironment. The objective of this study was to determine whether niacin modulates systemic immunity in patients with newly diagnosed glioblastoma.

Methods

In a first-in-human phase I clinical trial (NCT04677049), we investigated the immunologic effects of niacin administration alongside standard-of-care surgery and chemoradiation in patients with newly diagnosed glioblastoma.

Results

Niacin treatment increases the frequencies of circulating memory T cells and natural killer cells while decreasing nonclassical monocytes. Furthermore, niacin elevated serum levels of the proinflammatory cytokine interleukin (IL)-12p70 and granulocyte colony-stimulating factor and reduced growth-regulated α protein.

Discussion

These data demonstrate that niacin induces systemic immunomodulatory effects in patients with glioblastoma, shifting the immune landscape toward an antitumor profile and supporting further evaluation of niacin as a potential therapeutic adjunct.

Trial Registration Information

This ongoing study was registered as NCT04677049 on March 1, 2021, with the first patient enrolled on March 18, 2021.

Classification of Evidence

This study provides Class IV evidence that niacin dose escalation modulates immune response in patients with glioblastoma treated with standard of care, including maximal safe resection, concurrent radiation and temozolomide, and adjuvant temozolomide administration. This is a Class IV study because it is an open-label trial with no blinding or comparison group.

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Supplementary Material

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Glossary

DLT = dose-limiting toxicity; **G-CSF** = granulocyte colony-stimulating factor; **MDSC** = myeloid-derived suppressor cell; **PBS** = phosphate buffered saline; **RFU** = relative fluorescence unit.

Introduction

Glioblastoma (GBM) is the most common and deadly primary malignant brain tumor in adults. Maximal safe resection, followed by radiotherapy plus concomitant and adjuvant temozolomide, is the standard of care for patients with newly diagnosed GBM.[1] Despite this multimodality therapy, recurrence is inevitable and median survival remains approximately 15 months.[2] More effective therapies for GBM are urgently needed.

Immunotherapies such as immune checkpoint blockade have radically improved patient outcomes in solid tumors such as melanoma and non–small cell lung cancer but have limited success in GBM.[3] GBM demonstrates de novo resistance to immune checkpoint blockade, due in part to a potently immunosuppressive tumor microenvironment.[4,5] The immunosuppression in patients with GBM is also manifest in the peripheral blood, with reduced $CD4^+$ and $CD8^+$ T-cell and natural killer (NK) cell frequencies, coupled with increased myeloid-derived suppressor cells (MDSCs).[6,7] Dexamethasone administration, commonly used to manage peritumoral edema in patients with GBM, exacerbates these changes.[8] Thus, immunomodulatory therapies that sway the immunosuppressive microenvironment toward immunostimulatory phenotypes are highly desirable and could influence immune phenotypes within the tumor itself as well as in the peripheral blood.

Niacin (vitamin B3) has been shown by our group to not only increase the immunostimulatory behavior of immune cells in the GBM microenvironment but also decrease tumor size and prolong the survival of GBM-bearing mice.[9] Its candidacy as a novel anti-GBM treatment is further strengthened by its favorable side-effect profile in patients, having already been FDA-approved for use in hyperlipidemia and pellagra at substantial doses.[10] Given its relatively low cost compared with other novel therapeutics and high accessibility, niacin warrants investigation in a clinical trial alongside standard-of-care treatment in GBM.

In this article, we report the immunologic results of a first-in-human, phase I trial of niacin administration in patients with newly diagnosed GBM (NCT04677049). We find that niacin administration alters both adaptive and innate immune cell frequencies along with cytokine profiles in an antitumor direction, demonstrating its promise in modulating immune responses in GBM. This study investigates the use of niacin in CNS malignancies, an area that has received little prior clinical evaluation.

The primary research question being addressed in this study is whether niacin modulates the immune response in patients with newly diagnosed GBM who undergo standard-of-care maximal safe resection and chemoradiation. In addition, we investigate which components of the peripheral innate and adaptive immune system are modulated.

Methods

Study Design

This study was an open-label, phase I clinical trial that investigated the safety, tolerability, and preliminary immune activity of controlled-release niacin (NiacinCRT, Designs for Health, Palm Coast, FL) alongside standard-of-care treatment in patients with newly diagnosed GBM. This study uses an intrapatient dose-escalation design, detailed as additional data in eTable 1 and the "Treatment Administration" section.

Study Population

Eligible patients at the University of Calgary were ≥18 and ≤75 years of age with newly diagnosed, histopathologically confirmed GBM treated with standard-of-care maximal safe debulking (or biopsy, if maximal safe debulking was not possible), concurrent radiation and temozolomide, and adjuvant temozolomide administration. Patients were enrolled between March 18, 2021, and June 30, 2023. Patients were also required to have an Eastern Cooperative Oncology Group performance status of 0–2 and adequate hematologic, renal, and hepatic function. Exclusion criteria included patients with a known hypersensitivity to niacin or any component of controlled-release niacin. Full inclusion and exclusion criteria are listed online within the registry.[1] All patients were treated with controlled-release niacin, which herein will be referred to simply as niacin.

Treatment Administration

Niacin was administered as an oral daily dose, initiated 7 days before concurrent radiation and temozolomide treatment. The niacin dose was escalated in each patient every 4 weeks, if tolerated. Patients were monitored for dose-limiting toxicities (DLTs) after the first administration of niacin. The doses of niacin tested were 500 mg, 1,000 mg, 1,500 mg, 2,000 mg, and 2,500 mg daily. Escalation to the next dose level proceeded if no DLTs were observed. While the original dose-escalation design included a higher dose level of 3,000 mg daily, dose-limiting grade 3 thrombocytopenia (n = 1) and grade 3 hepatotoxicity (n = 1) identified at the 2,500 mg dose determined that future patients only received up to 2,000 mg of niacin daily.

Clinical Trial Specimens

We obtained peripheral blood samples from patients with GBM at baseline prior to niacin administration and at each dose level of niacin during the phase I clinical trial (NCT04677049) in accordance with institutional review board approval.

Blood Processing for Serum Collection and Multiplex Assays

One VACUETTE tube containing a serum clot activator (Greiner Bio-One, Monroe, NC) was used to collect 5–9 mL of whole blood from patients at baseline and at each dose level of niacin. After centrifugation of whole blood, serum was collected from the top layer and stored at −20°C. The Human Cytokine Panel A 48-Plex Discovery Assay (MilliporeSigma, Burlington, MA) was used to test serum samples in duplicate. Additional data in eTable 2 list the cytokines, chemokines, and growth factors included in this analysis.

Blood Processing and Sample Preparation for Flow Cytometry

A BD Vacutainer Heparin Tube (Becton, Dickinson and Company, Franklin Lakes, NJ) was used to collect 5 mL of whole blood for flow cytometry. Approximately 45 mL of Red Blood Cell Lysis Buffer (Roche, Basel, Switzerland) was added to the whole blood and incubated at room temperature until the solution became translucent. Next, the whole blood underwent centrifugation at 1,200 rpm for 5 minutes at room temperature, the supernatant was decanted, and the remaining cells were resuspended in 50 mL of phosphate buffered saline (PBS), followed by centrifugation again at 1,200 rpm for 5 minutes to wash the cells. The cells were counted and resuspended in PBS at a concentration of 1×10^6/mL. For flow cytometry, 1×10^6 cells were added to each round-bottomed polystyrene test tube (Corning Inc., Corning, NY). Live/Dead Blue (Invitrogen, Thermo Fisher Scientific, Waltham, MA) was prepared according to the manufacturer's protocol and added to the cells at a 1:800 dilution. The tubes were incubated at 4°C for 30 minutes. Cells were then washed with PBS and centrifuged at 1,200 rpm for 5 minutes at 4°C. After this, True-Stain Monocyte Blocker (BioLegend, San Diego, CA) was added and the tubes were incubated for 10 minutes at 4°C. Cells were then washed with PBS and centrifuged at 1,200 rpm for 5 minutes at 4°C. Next, cells were resuspended in an antibody cocktail and incubated for 20 minutes at 4°C (eTable 3 lists antibodies and dilution factors). Tubes were washed and centrifuged at 1,200 rpm for 5 minutes at 4°C. Afterward, the cells were fixed using 1% buffered formalin or 4% paraformaldehyde for 20 minutes at 4°C. The cells were washed and resuspended in PBS before being analyzed via flow cytometry within 48 hours. All experiments included unstained cells as controls. Peripheral blood mononuclear cells (PBMCs) or UltraComp eBeads Plus Compensation Beads (Invitrogen, Thermo Fisher Scientific, Waltham, MA) were used as reference controls for the antibodies (additional data in eTable 3). Positive and negative controls for Live/Dead Blue and single-stain controls were run every 6 months during the trial. Fluorescence-minus-one controls for each stain using PBMCs from healthy control patients were analyzed to assist in gating.

Advanced Spectral Flow Cytometry and Analysis

Cells were analyzed using a Cytek Aurora spectral flow cytometer (Cytek Biosciences, Fremont, CA) and SpectroFlo software, following the manufacturer's recommended settings and compensation protocols. Unmixed data were then gated and analyzed in FlowJo version 10.10.0 (BD Biosciences, Ashland, OR). Single cells were gated using forward-scatter area and height, followed by side-scatter area and height. Next, live cells were gated, followed by gating of the immune cell population of interest (additional data in eTable 4[11-28]). Individual gates were adjusted for each sample because of between-patient variability. Data are presented as the percent frequency of live cells to normalize results between patients. A representative example of gating is shown in eFigure 1.

Statistical Analyses

Cytokine-level changes were analyzed using Wilcoxon matched-pairs signed-rank tests in GraphPad Prism 10 for Windows version 10.4.1 (San Diego, CA).

Immune cell frequency analysis during niacin dose escalation was performed using a linear mixed-effects model, with immune cell frequencies as a dependent factor and niacin dose escalations, sex, and age as covariates. We used random intercepts for individual patients to account for differences in baseline immune cell frequencies. A Bonferroni post hoc test was performed to adjust for multiple comparisons. SPSS version 29.0 (Armonk, NY) was used. GraphPad Prism 10 for Windows version 10.4.1 (Dotmatics, San Diego, CA) generated the graphical representations.

Standard Protocol Approvals, Registrations, and Patient Consents

The Study Protocol and Statistical Analysis Plan are available in the eSAP. The protocol, informed consent forms, any information given to patients, and relevant supporting information were submitted, reviewed, and approved by the Health Research Ethics Board of Alberta (certificate number HREBA.CC-20-0402) before this study was initiated. This trial is being conducted in accordance with the International Conference on Harmonization-Good Clinical Practice Guidelines, the Declaration of Helsinki, and the Tri-Council Policy Statement.

Data Availability

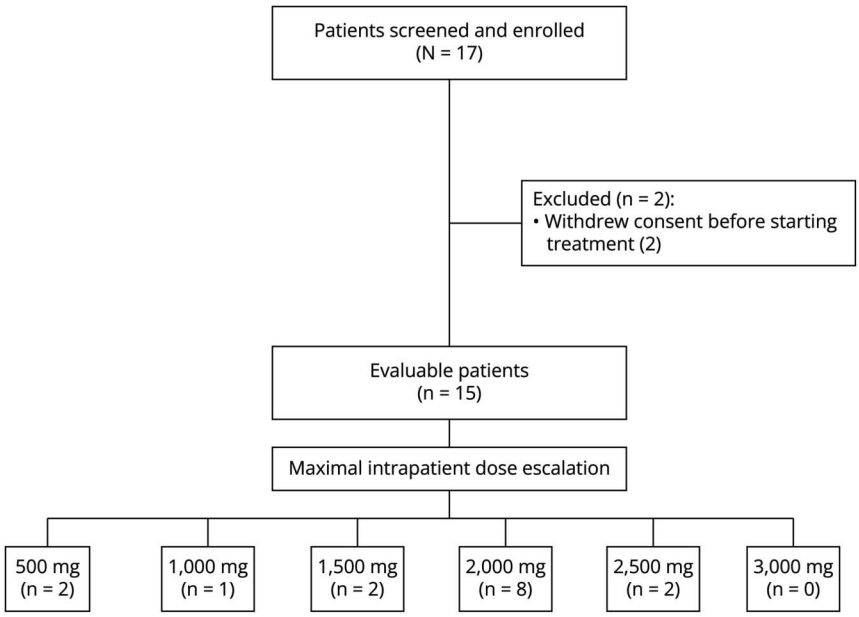
All data are available on reasonable request.

Results

Patient Demographics and Baseline Characteristics

A total of 17 patients were screened for eligibility at the University of Calgary, and 15 patients were enrolled between

Figure 1 Schematic of Study Enrollment



March 18, 2021, and June 30, 2023 (Figure 1). The aggregate demographic and baseline characteristics of all patients enrolled are given in Table 1. The median age of patients was 57 years, and 40% were women. A gross total resection was achieved in 67% of patients while 7% underwent biopsy only. All patients had newly diagnosed, histopathologically confirmed GBM and thus were chemoradiation naïve, with 7% of patients using steroids at baseline. Hypermethylation of the O6-methylguanine–DNA methyltransferase (MGMT) promoter was present in 47% of patients. At the time of data analysis, the median follow-up duration was 16 months (range 5–25 months).

Table 1 Patient Demographics and Baseline Characteristics (n = 15)

Characteristic	Patients (n = 15), no. (%)
Median age (range), y	57 (37–68)
Sex	
Male	9 (60)
Female	6 (40)
MGMT gene promoter methylation status	
Methylated	7 (47)
Unmethylated	8 (53)
Type of surgery	
Gross total resection	10 (67)
Subtotal resection	4 (27)
Biopsy	1 (7)
Baseline dexamethasone use ≥1.5 mg per d	1 (7)

Niacin Dose Effects on Immune Cell Frequencies of Patients With GBM

To characterize the immune response to niacin administration, we analyzed the serum samples of patients via advanced spectral flow cytometry at baseline and after each niacin dose escalation (500 mg, 1,000 mg, 1,500 mg, 2,000 mg, and 2,500 mg). A linear mixed-effects model incorporating dose, age, and sex was used to model drug doses as a continuous fixed effect and to account for individual variability. We found that nonclassical monocytes ($CD16^+CD11c^+CD14^{low}HLADR^{low}$) were associated with a statistically significant decrease with niacin dose escalation ($p = 0.019$*) while memory T-cell ($CD3^+CD8^+CX3CR1^-$) and natural killer cell ($CD14^-CD16^+CD33^-CD86^+CD56^+CD3^-$) frequencies increased ($p = 0.020$* and $p = 0.027$*, respectively; Table 2 and Figure 2). Neutrophil ($CD14^-CD15^+CD16^+CD64^+CD66b^+$) frequency trended toward a decrease in response to niacin dosing. Frequencies of natural killer T cells, regulatory T cells, effector T cells such as central memory and effector memory T cells, MDSCs, classical and intermediate monocytes, macrophages, and dendritic cells were also investigated, but no significant associations with niacin dosing were found (additional data in eTable 5).

Age also independently affected memory T-cell and NK cell frequencies ($p = 0.003$** and $p = 0.013$*, respectively; Table 2). Interactions between dose, age, and sex were also present in several immune cell populations, as given in eTable 6.

Table 2 Linear Mixed-Effects Model Results Investigating the Effect of Niacin Dose, Sex, and Age on Immune Cell Frequencies (n = 13; the Samples of 2 Patients Were Lost During Transport—Both Patients Had Received 1 Month or Less of Niacin Treatment)

Immune cell population	Parameter	Degrees of freedom	*F*	*p* Value
Neutrophils				
	Niacin dose	13.453	2.937	0.061
	Sex	8.784	1.939	0.198
	Age	21.969	1.178	0.289
Memory T cells				
	Niacin dose	14.57	4.1	0.02[a]
	Sex	9.122	0.744	0.41
	Age	19.823	11.624	0.003[b]
Nonclassical monocytes				
	Niacin dose	13.108	4.327	0.019[a]
	Sex	9.028	0.079	0.785
	Age	12.261	0.562	0.468
NK cells				
	Niacin dose	14.303	3.853	0.025[a]
	Sex	8.767	0.415	0.536
	Age	19.556	7.416	0.013[a]

A Bonferroni post hoc test was performed to adjust for multiple comparisons, with a p value <0.05 considered significant.

Niacin Administration Alters the Cytokine Milieu in Patients With GBM

Serum cytokine levels were quantified at baseline and after dose escalation to 2,000 mg (8 patients achieved this dose) using the Human Cytokine/Chemokine Panel A 48-Plex Discovery Assay (MilliporeSigma, Burlington, MA). Interleukin-12 subunit p70 (IL-12p70) and granulocyte colony-stimulating factor (G-CSF) were significantly elevated (IL-12p70 levels changed from 33.97 ± 44.16 relative fluorescence units [RFU] to 59.78 ± 95.02 RFU, $p = 0.0078^{**}$, and G-CSF levels changed from 70.81 ± 40.7 RFU to 104.2 ± 80.2 RFU, $p = 0.023^{*}$, respectively), while growth-regulated α protein (GROa), also known as C-X-C motif chemokine ligand 1, was downregulated (GROa levels changed from 446.7 ± 226.2 RFU to 310.0 ± 159.0 RFU, $p = 0.039^{*}$; Figure 3). IL-5 and IL-27 trended toward upregulation (IL-5 levels changed from 65.81 ± 51.35 RFU to 134.1 ± 138.5 RFU, $p = 0.055$, and IL-27 levels changed from 814.4 ± 704.1 RFU to 2,110 ± 2204 RFU, $p = 0.078$, respectively) while monokine induced by gamma interferon (MIG), also known as CXCL9, trended downward (MIG levels changed from 3,044 ± 1827 RFU to 2,295 ± 1460 RFU; $p = 0.078$; Figure 3). No significant differences were observed for the remaining 42 cytokines assayed, including for IL-12p40 (IL-12p40 levels were 47.97 ± 48.54 RFU at baseline and 88.47 ± 120.3 RFU after dose escalation to 2,000 mg, $p = 0.1094$; eFigure 2).

Classification of Evidence

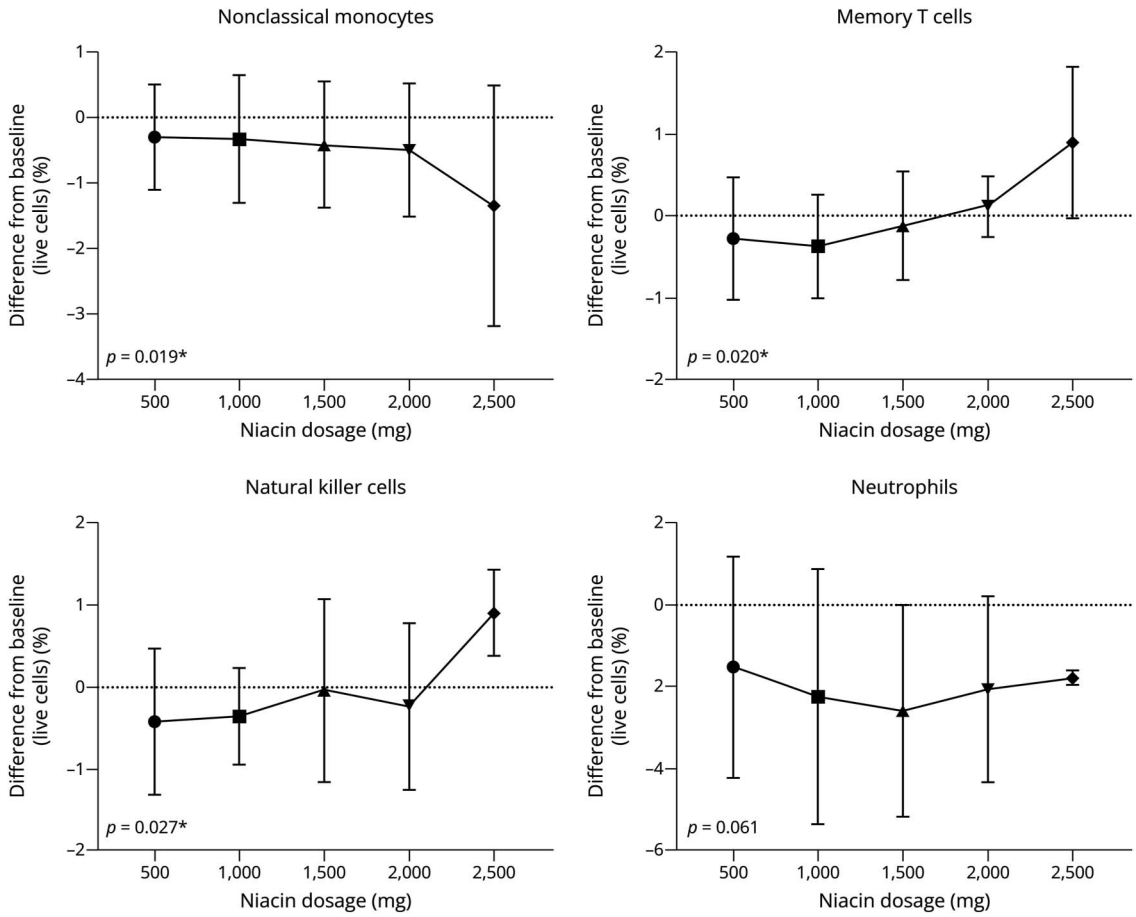
This study provides Class IV evidence that niacin dose escalation modulates immune response in patients with glioblastoma treated with standard of care, including maximal safe resection, concurrent radiation and temozolomide, and adjuvant temozolomide administration. This is a Class IV study because it is an open-label trial with no blinding or comparison group.

Discussion

Although immunotherapies have revolutionized the care of many cancer patients with solid tumors, efficacy has yet to be demonstrated in GBM.[3] GBM is associated with a potently immunosuppressive microenvironment that thwarts experimental immunotherapies and standard-of-care treatments alike. Immunomodulators that alleviate the immunosuppressive nature of the GBM microenvironment would be valuable adjuncts not only to current treatments but also in increasing the effectiveness of immunotherapy.

This study is based on supportive but early preclinical evidence that niacin is an immunostimulant in GBM, decreases tumor burden, and improves overall survival.[9] Patient bioassays of our phase I trial demonstrate for the first time that

Figure 2 Serum Immune Cell Frequencies

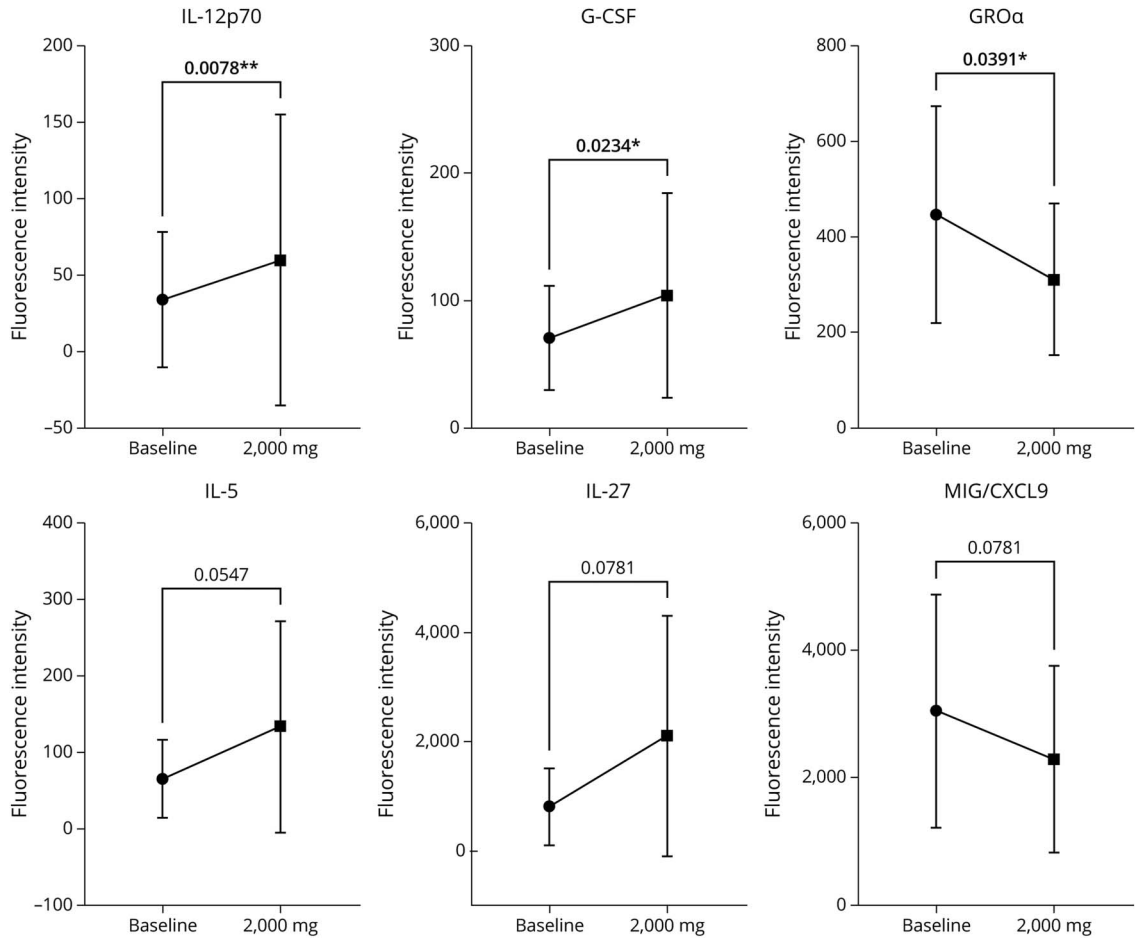


Serum immune cell frequencies after niacin dose escalation in patients with newly diagnosed GBM after surgery (n = 13; the samples of 2 patients were lost during transport—both patients had received 1 month or less of niacin treatment). A linear mixed-effects model, with a Bonferroni post hoc test performed to adjust for multiple comparisons, was used to analyze the data. A p value of <0.05 was considered significant (p = 0.019* for nonclassical monocytes, p = 0.020* for memory T cells, p = 0.027* for natural killer cells, and p = 0.061 for neutrophils). GBM = glioblastoma.

niacin modulates immune cell frequencies and serum cytokine levels in patients with GBM. Immune cell subtype frequencies shifted toward an antitumor profile—memory T-cell and NK cell populations increased while nonclassical monocyte numbers decreased. Nonclassical monocytes are associated with immunosuppression in patients with GBM,[29] upregulate expression of immune checkpoint molecules such as PD-L1,[30] and are associated with shorter overall survival.[31] Myeloid cells such as nonclassical monocytes, which differentiate into tissue-resident macrophages, are critical contributors to the immunosuppressive microenvironment of GBM. Therefore, therapies that reduce this myeloid subpopulation are valuable for GBM treatment. Memory T cells are generally inhibited in GBM,[32] hampering tumor immunosurveillance whereby the immune system continuously monitors and eliminates emerging cancer cells. Similarly, NK cells are sparse in GBM[33] but have potent cytotoxic activity against cancer cells.[34] Increasing the abundance of memory T cells has been demonstrated to potentiate immune checkpoint blockade,[35] suggesting that niacin may enhance immunosurveillance in GBM. NK cell administration is also being actively explored as a treatment to increase cytotoxicity against GBM cells (NCT06687681, NCT04991870)—a strategy that may be augmented with niacin administration. Of note, there does appear to be a dose-dependent response, with higher niacin doses corresponding to increased immunophenotypic changes. Together, these immune cell frequency changes constitute a favorable shift in the immune profile and suggest that niacin may be a useful immunostimulant in patients with GBM.

Niacin administration was also associated with changes in serum cytokine levels. IL-12 is a powerful proinflammatory cytokine with antitumor properties. For instance, IL-12 enhances CAR-T cell–mediated cell kill against murine glioma[36] and prolongs survival in glioma-bearing mice by inducing interferon-gamma synthesis in immune cells while reducing MDSC frequencies.[37] IL-12 can also increase $CD4^+$ and $CD8^+$ T-cell and activated microglia infiltration.[38,39] However, the clinical application of IL-12 has been limited because of off-target effects from cytokine release syndrome.[40] In our study, the increase in IL-12p70, the fully functional,

Figure 3 Serum Cytokine Levels



Comparison of serum cytokine, chemokine, and growth factor levels at baseline and after administration of 2000 mg of niacin. Data were analyzed using Wilcoxon matched-pairs signed rank tests. A p value of <0.05 was considered significant.

heterodimeric form of IL-12, was tolerable in patients. Levels of IL-12p40, an antagonist to IL-12p70 and a chemotactic molecule for potentially immunosuppressive macrophages,[41] remained unchanged, suggesting that IL-12p70 activity was not hampered with a concomitant increase in IL-12p40 after niacin administration. In addition, levels of G-CSF were elevated by niacin. Whether G-CSF is beneficial or harmful to patients with GBM is controversial. Cell culture studies suggest that G-CSF enhances the proliferation, migration, and invasion of glioma cells.[42] However, several in vivo studies since have suggested that G-CSF elevation promotes antitumor activities. In mutant isocitrate-dehydrogenase 1 gliomas, G-CSF reprogrammed bone marrow granulopoiesis and led to the infiltration of nonimmunosuppressive myeloid cells within gliomas, enhancing immunotherapy efficacy.[43] Similarly, concurrent administration of G-CSF and oncolytic viruses improved survival of osteosarcoma-bearing mice, in part by increasing the number of tumor-infiltrating lymphocytes and decreasing T-cell exhaustion.[44] Previous findings in patients with GBM have shown that lower neutrophil-to-lymphocyte ratios, before and during concurrent chemoradiation, are associated with longer overall survival.[45] This study suggests a trend toward a decreased neutrophil frequency with niacin treatment. However, G-CSF is used to treat chemotherapy-induced neutropenia in other cancers by shifting hematopoiesis toward granulocytic lineages such as neutrophils.[46] This discrepancy may be explained by the multiple mechanisms needed to generate neutrophilia. Although serum G-CSF was elevated with niacin administration, GROa, pivotal in recruiting neutrophils, was decreased. Thus, despite elevated G-CSF, the decrease in GROa may explain the lower neutrophil frequencies observed. Finally, GROa also enhances the proliferation, motility, and invasiveness of glioma cells[47]; increases myeloid cell infiltration; and disrupts $CD8^+$ T-cell accumulation within GBM.[48] Thus, decreasing GROa levels could be beneficial to patients with GBM. Overall, niacin swayed serum cytokine levels toward an antitumor direction.

Niacin is an attractive immunomodulator to use in GBM for many high-impact reasons. Niacin is an off-patent vitamin that can be mass produced at low cost and used widely. Niacin has

an established safety profile, with doses <2500 mg proposed for use in this study falling within FDA-approved guidelines for dyslipidemia treatments. Niacin is also being used concurrently with the Stupp protocol[2] in our trial, offering no disruption to the first-line regimen recommended for patients with GBM worldwide.

Nevertheless, further research including completion of our ongoing phase I/II trial is required before definitive conclusions can be made. The limitations of this study must also be addressed. First, findings in this small cohort of patients may not be replicated in a larger population. Thus, we will continue expanding our cohort to ensure the generalizability of results. Second, systemic levels of immune cells and their activity may not be reflective of those infiltrating the tumor tissue itself. Future studies should incorporate paired systemic and local tissue examinations of immune profiles in response to niacin treatment. There is precedence that systemic measures of immune function correlate with GBM patient outcomes[31] and evidence that immune activity measured in the periphery is reflective of the administration of immunotherapies[49,50] and the level of immunosuppression.[51] However, this evidence is not specific to niacin administration, and thus, our results must be interpreted with this caveat in mind. Third, serum availability was not comprehensive because of the inherent difficulties of translational research in human participants, including failures of sample collection or lost samples. In addition, not all patients were able to tolerate the same degree of dose escalation. However, most were able to reach a dose of 2000 mg. We will be commencing the phase II portion of the trial to determine whether niacin is efficacious at this dose.

In summary, our study is the first to report on the immunomodulatory effects of niacin in patients with GBM. The addition of niacin to standard chemoradiotherapy alters the immune profile of patients with GBM toward an antitumor phenotype. Serum immune cell frequency changes, including an increase in memory T cells and NK cells and a decrease in nonclassical monocytes, may be favorable to the patient. Cytokine levels also reflect favorable changes, with an upregulation of IL-12p70 and G-CSF and a downregulation of GROa. Future planned analyses of progression-free and overall survival, along with reporting of adverse outcomes, will help determine the viability of niacin as an adjunct to chemoradiation and potentially nominate niacin as a valuable addition to other immunotherapies targeted against GBM.

Author Contributions

C.C. Poon: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. K.M. Hagen: major role in the acquisition of data. S. Sarkar: major role in the acquisition of data; study concept or design. R. Mirzaei: study concept or design. C. Silva: major role in the acquisition of data. A. Ueno: drafting/revision of the manuscript for content, including medical writing for content. P. de Robles: drafting/revision of the manuscript for content, including medical writing for content. G. Roldan-Urgoiti: drafting/revision of the manuscript for content, including medical writing for content. V.W. Yong: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NN for full disclosures.

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