Lymphopenia in Glioblastoma

- Final Report on NCCTG N0877 (Alliance): A Phase II Randomized, Placebo-Controlled Trial of Chemoradiotherapy with or without Dasatinib for Glioblastoma
- ATP11B triggers the infiltration of T cells into GBM and intensifies anti-GBM immunity by upregulating and externalizing S1PR1
- FcRn-silencing of IL-12Fc prevents toxicity of local IL-12 therapy and prolongs survival in experimental glioblastoma
- Peripheral biomarkers predict survival in patients with glioblastoma treated with temozolomide
- Tumor-infiltrating and circulating B cells mediate local and systemic immunomodulatory mechanisms in Glioblastoma
- Effect of glioblastoma and brain radiotherapy on T-lymphocyte subpopulations in rodents
- Reduced Treatment Volumes for Glioblastoma Associated With Lower Rates of Radionecrosis and Lymphopenia: A Pooled Analysis
- Flow cytometry detection and quantification of circulating leukocyte subpopulations in mice after brain irradiation

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Lymphopenia, a condition characterized by a low count of lymphocytes (a type of white blood cell), has been associated with various cancers, including glioblastoma.

Factors

Lymphopenia in glioblastoma patients can arise due to several factors:

Tumor-induced immune suppression: Glioblastoma tumors can create a suppressive microenvironment within the brain, inhibiting the function of immune cells, including lymphocytes.

Treatment-related effects: Therapies such as chemotherapy and radiation, which are commonly used to treat glioblastoma, can also suppress the immune system and lead to lymphopenia as a side effect.

Systemic effects of the disease: Glioblastoma can exert systemic effects on the body, impacting immune function beyond the central nervous system.

Malnutrition and other complications: Advanced glioblastoma can lead to complications such as malnutrition, which may indirectly contribute to lymphopenia.

Lymphopenia in glioblastoma patients may have clinical implications, as it can compromise the body's ability to mount an effective immune response against the tumor. Strategies to mitigate lymphopenia and enhance immune function in glioblastoma patients are areas of active research, with immunotherapy emerging as a promising approach to bolstering the immune system's ability to target and destroy cancer cells.

Development of post-RT lymphopenia is associated with the addition of TMZ and baseline

lymphopenia and not with RT alone in patients treated with short-course radiation. However, regardless of MGMT status, only baseline lymphopenia is associated with worse OS, which may be considered as a prognostic biomarker for elderly glioblastoma outcome patients [1)]

We now appreciate the value of the immunomodulatory effects of radiation that may be important to overall therapeutic success in some patients with this primary brain tumor. Although potentially beneficial immune-stimulating properties of radiotherapy treatment have been the focus of recent study, this modality is actually at the same time associated with the depletion of lymphocytes, which are crucial to the defense against neoplastic development and progression. In a review, Kleinberg et al. described the association of systemic lymphopenia with poor tumor outcome, present evidence that radiotherapy is an important contributing cause of lymphodepletion, describe the systemic immune context of tumor and brain injury that contributes to immunosuppression, describe other contributing factors to lymphopenia including concomitant medications and treatments, and speculate about the role of the normal physiologic response to brain injury in the immunosuppressive dynamics of Glioblastoma. Radiotherapy is one significant and potentially actionable iatrogenic suppressor of immune response that may be limiting the success of therapy in Glioblastoma and other tumor types. Altered strategies for radiotherapy more permissive of a vigorous antineoplastic immune response may improve the outcome for malignancy [2)].

Lymphopenia is a frequent event during Glioblastoma (Glioblastoma) disease progression and treatment. Treatment-related lymphopenia is profound and prolonged and can be used as a prognostic factor for Glioblastoma patients [3)].

Lymphopenia in patients with glioblastoma (Glioblastoma) is related to treatment as well as disease progression. A retrospective study investigated the prevalence, influencing factors, recoverability, and clinical significance of lymphopenia in Glioblastoma patients treated with concomitant chemoradiotherapy (CCRT).

A total of 219 patients with newly diagnosed Glioblastoma who had received at least 3 cycles of adjuvant temozolomide (TMZ) followed by CCRT with TMZ were enrolled. Serial data on complete blood cell counts, including differential cell counts, were collected just before a new phase and before every treatment cycle of the regimen. Relationships between white blood cell (WBC) variable changes and treatment modalities as well as survival were analyzed. Lymphopenia was classified using the definition of the Common Terminology Criteria for Adverse Events version 5.0.

A total of 92 patients (42.0%) showed decreased levels of lymphocytes (< 1500/μL) at baseline. The WBC count, absolute neutrophil count, lymphocyte count, and neutrophil-to-lymphocyte ratio were all significantly decreased after RT/TMZ treatment and did not recover during the adjuvant TMZ period. However, these metrics all began to recover 3 months after the last TMZ cycle, except for the lymphocyte count. The proportion of lymphopenia patients (< 1500 lymphocytes/μL) increased to 74.8% after RT/TMZ and remained steady at approximately 71.5% (range 63.7-75.3%) throughout the management period. Moreover, the number of patients with grade 3 lymphopenia (< 500 lymphocytes/μL) also increased significantly after treatment to reach 2.9% (from 0.9% at baseline). Statistically, 75.7% of lymphopenia patients were predicted to recover in a median time of 240.3 days (95% confidence interval ± 104.7 days) after TMZ withdrawal. There were no dose-dependent relationships between RT or TMZ and lymphopenia. Grade 3 (< 500 lymphocytes/μL) lymphopenia measured at 1 month after RT/TMZ predicted significantly reduced survival (13.0 months vs. 19.5

months, p = 0.011).

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Outcome of lymphopenia in glioblastoma

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- NANO-GBM trial of AGuIX nanoparticles with radiotherapy and temozolomide in the treatment of newly diagnosed Glioblastoma: Phase 1b outcomes and MRI-based biodistribution
- Nomogram for radiation-induced lymphopenia in patients receiving intensity-modulated radiotherapy based-chemoradiation therapy for newly diagnosed glioblastoma: A multi-institutional study
- LymphoDose: a lymphocyte dose estimation framework-application to brain radiotherapy
- Systematic review and pooled analysis of the impact of treatment-induced lymphopenia on survival of glioblastoma patients

Several single-institution studies have linked lymphopenia with poor survival outcomes.

The outcome of lymphopenia in glioblastoma patients can vary depending on several factors, including the extent of lymphopenia, the stage of the disease, the effectiveness of treatment, and the overall health status of the patient. Here are some considerations regarding the outcome:

Impact on immune response: Lymphopenia can compromise the body's immune response against the glioblastoma tumor. Lymphocytes play a crucial role in immune surveillance and tumor defense, so a low lymphocyte count may reduce the ability of the immune system to recognize and attack cancer cells.

Treatment response: Lymphopenia may influence the response to treatment. Studies have suggested that glioblastoma patients with lower lymphocyte counts may have poorer outcomes following standard treatments such as surgery, chemotherapy, and radiation therapy.

Survival: Some research indicates that lymphopenia at the time of diagnosis or during treatment may be associated with shorter overall survival in glioblastoma patients. This suggests that lymphopenia could be a prognostic factor for disease progression and survival outcomes.

Influence of immunotherapy: Immunotherapy, which aims to enhance the body's immune response against cancer, is an active area of research in glioblastoma treatment. Lymphopenia may affect the effectiveness of immunotherapy, as it relies on a functional immune system to exert its anti-tumor effects. Strategies to overcome lymphopenia and improve immune function, such as adoptive cell therapies and cytokine-based treatments, are being explored to optimize the outcomes of immunotherapy in glioblastoma patients.

Overall, while lymphopenia in glioblastoma patients may be associated with poorer outcomes, its

precise impact and clinical significance require further investigation. Strategies to monitor and manage lymphopenia, along with advancements in immunotherapy, hold promise for improving treatment outcomes in this challenging disease.

Saeed et al. from the University of Maryland School of Medicine, performed a systematic review and pooled analysis to evaluate the association between lymphopenia and overall survival (OS) for GBM patients undergoing chemotherapy and radiation therapy (RT).

Following PRISMA guidelines, a systematic literature review of the MEDLINE database and abstracts from ASTRO, ASCO, and SNO annual meetings was conducted. A pooled analysis was performed using inverse variance-weighted random effects to generate a pooled estimate of the hazard ratio of association between lymphopenia and OS.

Ten of 104 identified studies met inclusion criteria, representing 1,718 patients. The lymphopenia cutoff value varied (400-1100 cells/uL) and as well as the timing of its onset. Studies were grouped as time-point (i.e., lymphopenia at approximately 2-months post-RT) or time-range (any lymphopenia occurrence from treatment-start to approximately 2-months post-RT. The mean overall pooled incidence of lymphopenia for all studies was 31.8%, and 11.8% vs. 39.9% for time-point vs. time-range studies, respectively. Lymphopenia was associated with increased risk of death, with a pooled HR of 1.78 (95% CI 1.46-2.17, $P < 0.00001$) for the time-point studies, and a pooled HR of 1.38 (95% CI 1.24-1.55, $P < 0.00001$) for the time-point studies. There was no significant heterogeneity between studies.

These results strengthen observations from previous individual single-institution studies and better defines the magnitude of the association between lymphopenia with OS in GBM patients, highlighting lymphopenia as a poor prognostic factor [5)]

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