Effect Of Pretreatment Lymphopenia On Survival In Patients With Recurrent Glioblastoma Receiving Immunotherapy

Orin Bloch MD; Yelena S. Fuks BS; Manish Kumar Aghi MD PhD; Michael William McDermott MD; Mitchel S. Berger MD; Andrew E. Sloan MD; Jeffrey N. Bruce MD; Andrew T. Parsa MD PhD

Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University

Introduction

Glioma-induced lymphopenia and lymphocyte dysfunction are well-recognized factors contributing to immunosuppression in patients with glioblastoma (GBM). Despite a long history of studying this immunosuppression, there have been few reports demonstrating that lymphocyte dysfunction independently predicts patient outcomes. Immunosuppression is a particularly important factor for patients receiving immunotherapy. We, therefore, analyzed the impact of lymphopenia on outcomes of patients receiving an autologous tumor vaccine for recurrent GBM.

Methods

As part of a prospective, multi-centered, phase II study, patients with recurrent GBM received autologous vaccine after gross-total resection of their tumors. The primary clinical endpoint was overall survival. Pre-operative blood samples were taken from all patients to measure the complete blood count (CBC) and differential, including the absolute lymphocyte count (ALC). In this analysis, survival outcomes were evaluated relative to the median ALC by univariate Kaplan-Meier analysis and multivariate Cox proportional hazards modeling.

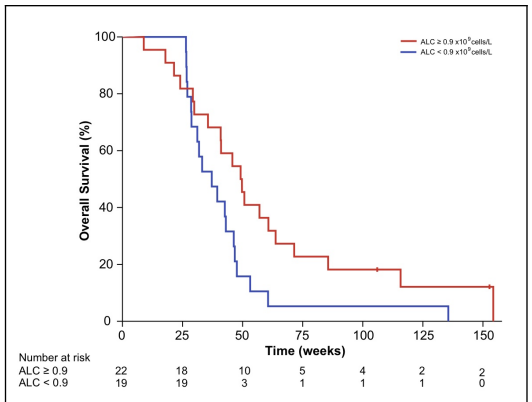

Figure 1: Kaplan-Meier estimate of overall survival stratified by ALC

Results

A total of 41 patients with recurrent GBM underwent resection and received a median of 6 doses of autologous vaccine. Median overall survival for the entire cohort was 42.6 weeks (95% CI 34.7-50.5). The median ALC was 0.9 x10^3 cells/uL, with 27/41 (66%) patients having lymphopenia according to the clinical laboratory standard (ALC < 1.0). When stratifying patients by ALC relative to the median value, patients with an ALC = 0.9 had significantly improved survival compared to patients with an ALC < 0.9 (49.1 vs. 37.1 weeks; log-rank p=0.039). In a proportional hazards model including age, KPS, number of vaccine doses, and lymphocyte counts, an ALC = 0.9 was an independent positive predictor with a hazard ratio of 0.85 (95% CI 0.73-0.99, p=0.036).

Variable	Hazard Ratio (95% CI)	p Value
Age (per 1-yr increment)	1.01 (0.97 – 1.06)	0.58
Gender		
Female	0.76 (0.27 – 2.10)	0.59
Male	1.0	
KPS		
70	2.28 (0.70 – 7.42)	0.17
80	0.65 (0.30 – 1.42)	0.28
90	1.0	
Vaccine Doses (per dose increment)	0.85 (0.73 – 0.99)	0.04
Absolute Lymphoctye Count		
Below median	4.02 (1.37 – 11.83)	0.01
Above/Equal to median	1.0	

Table 1: Proportional Hazards Model for Predictors of Outcome

Conclusions

Pretreatment lymphopenia may affect the outcomes of patients with recurrent GBM receiving immunotherapy. The implications of lymphopenia should be considered when selecting patients for future vaccine clinical trials.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) describe the effects of glioblastoma on lymphocyte counts and function, 2) describe the mechanism of action of adoptive immunotherapy for glioblasoma, 3) identify the impact of glioma-induce lymphopenia on immunotherapy outcomes.

References

1.Srivastava PK, Callahan MK, Mauri MM. Treating human cancers with heat shock protein-peptide complexes: the road ahead. Expert Opin Biol Ther. 2009; 9(2): 179-86.

2.Crane CA, Han SJ, Ahn B, Oehlke J, Kivett V, Fedoroff A, et al. Individual patient-specific immunity against high-grade glioma after vaccination with autologous tumor derived peptides bound to the 96 KD chaperone protein. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013; 19(1): 205-14.

3.Elliott LH, Brooks WH, Roszman TL. Cytokinetic basis for the impaired activation of lymphocytes from patients with primary intracranial tumors. J Immunol. 1984; 132(3): 1208-15.

4.Roszman TL, Brooks WH. Immunobiology of primary intracranial tumours. III. Demonstration of a qualitative lymphocyte abnormality in patients with primary brain tumours. Clin Exp Immunol. 1980; 39(2): 395-402.

5.Fecci PE, Mitchell DA, Whitesides JF, Xie W, Friedman AH, Archer GE, et al. Increased regulatory T-cell fraction amidst a diminished CD4 compartment explains cellular immune defects in patients with malignant glioma. Cancer Res. 2006; 66(6): 3294-302.

6.Fong B, Jin R, Wang X, Safaee M, Lisiero DN, Yang I, et al. Monitoring of regulatory T cell frequencies and expression of CTLA-4 on T cells, before and after DC vaccination, can predict survival in GBM patients. PLoS One. 2012; 7(4): e32614.