RESEARCH PAPER

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The natural killer cell response and tumor debulking are associated with prolonged survival in recurrent glioblastoma patients receiving dendritic cells loaded with autologous tumor lysates

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Recurrent glioblastomas (GBs) are highly aggressive tumors associated with a 6–8 mo survival rate. In this study, we evaluated the possible benefits of an immunotherapeutic strategy based on mature dendritic cells (DCs) loaded with autologous tumor-cell lysates in 15 patients affected by recurrent GB. The median progression-free survival (PFS) of this patient cohort was 4.4 mo, and the median overall survival (OS) was 8.0 mo. Patients with small tumors at the time of the first vaccination (< 20 cm^3; n = 8) had significantly longer PFS and OS than the other patients (6.0 vs. 3.0 mo, p = 0.01; and 16.5 vs. 7.0 mo, p = 0.003, respectively). $CD8^+$ T cells, $CD56^+$ natural killer (NK) cells and other immune parameters, such as the levels of transforming growth factor β, vascular endothelial growth factor, interleukin-12 and interferon γ (IFNγ), were measured in the peripheral blood and serum of patients before and after immunization, which enabled us to obtain a vaccination/baseline ratio (V/B ratio). An increased V/B ratio for NK cells, but not $CD8^+$ T cells, was significantly associated with prolonged PFS and OS. Patients exhibiting NK-cell responses were characterized by high levels of circulating IFNγ and E4BP4, an NK-cell transcription factor. Furthermore, the NK cell V/B ratio was inversely correlated with the TGFβ2 and VEGF V/B ratios. These results suggest that tumor-loaded DCs may increase the survival rate of patients with recurrent GB after effective tumor debulking, and emphasize the role of the NK-cell response in this therapeutic setting.

Introduction

Glioblastoma (GB) is the most aggressive type of primary brain tumor. Limitations regarding surgery, stemming from anatomical localization of the tumor and from its infiltrative nature, coupled to the partial resistance to multiple radio- and chemotherapeutic approaches lead to inevitable tumor recurrence. The overall survival (OS) time of GB patients receiving the standard treatment, which consists of surgery, concomitant radiotherapy and six or more cycles of temozolomide (TMZ) is 14.6 mo.[1] Several lines of evidence indicate that the immune system is capable of interacting with cancer cells to prevent their growth as well as to destroy established tumors.[2] However, attempts at utilizing the immune system to treat established tumors are confronted with consistent limitations, largely due to the immunosuppressive environment generated by malignant cells.[3] The induction of anti-GB immunity has been documented in vitro as well as in animal models.[4] Results from several early clinical trials using dendritic cell (DC) vaccines to initiate antitumor immune responses were promising,[5] indicating that antitumor immunity was induced in a fraction of patients and that immunological responders exhibited a prolonged survival rate as compared with control patients. Furthermore, increased levels of interferon γ (IFNγ) in the peripheral blood as well as in peripheral blood mononuclear cells (PBMCs) of GB patients have been associated with prolonged survival, and tumor debulking is known to decrease the expression of immunosuppressive

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Kaplan-Meier analysis was used to estimate PFS and OS. The Log-rank test was used to test the differences in PFS or OS in patients with different clinical, radiological or immunological parameters.

A multivariate analysis and a Cox proportional hazard regression model analysis were performed on the variables showing statistically significant differences in univariate analyses, in order to investigate their independent prognostic role. All statistical analyses were performed using MedCalc version 12.3.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Supplemental Material

Supplemental materials may be found here:
http://www.landesbioscience.com/journals/oncoimmunology/article/23401

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