Cellular immunotherapy directed against human cytomegalovirus as a novel approach for glioblastoma treatment

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Glioblastoma multiforme (GBM) has a very poor prognosis, despite multimodal therapy including surgery, radiation and chemotherapy. A novel adoptive immunotherapy that exploits the presence of cytomegalovirus antigens in malignant brain cancer cells has been shown to be safe and elicit potential clinical benefit for the treatment of recurrent GBM.

Cytomegalovirus Antigens as New Targets for Immunotherapy of GBM

GBM is a very aggressive form of human brain cancer with a low median survival of only slightly more than one year. Despite surgery, chemotherapy and radiation, GBM inevitably recurs and life expectancy is reduced to approximately six months. There is an urgent need for new treatment options that can improve patient outlook. Immunotherapies, both cellular and antibody based approaches, have great potential and are the focus of intense research. The discovery of CMV antigens in GBM tissues but not surrounding healthy brain cells, provided an exciting opportunity to boost pre-existing antiviral immunity to combat this brain malignancy. While CMV is not considered an oncogenic virus, it can promote several hallmarks of cancer, including deregulation of the cell cycle, immune evasion and stimulation of angiogenesis.

Adaptive Immunotherapy is Safe with Potential Clinical Benefit

We have shown previously that CMV specific cytotoxic T cells derived from seropositive GBM patients can be expanded in the laboratory following in vitro stimulation with synthetic CMV epitopes. Adoptive transfer of these cells into 1 patient with recurrent GBM was shown to be safe and coincident with long-term survival. We have now completed a formal assessment of CMV-specific immunotherapy as a Phase I clinical trial and provided autologous T-cell therapy to 10 patients with recurrent GBM (Fig. 1). This treatment was administered in 3 to 4 doses and proved to be completely safe with only mild to moderate side effects like headaches or fatigue. The overall survival since initial diagnosis ranged from 133 d to 2498 d with a median of 403 d. Most importantly, 4 out of the 10 patients that received at least 3 T-cell infusions, remained cancer free during the study period. The patient with the longest disease stabilization has not shown signs of tumor relapse to date, which is more than 4 y after receiving T-cell therapy. For the patients that did have tumor recurrence after T-cell therapy, we reported a median progression-free survival of 246 d, which is considerably longer than the expected life expectancy of 6 mo. While conclusions about survival need to be confirmed in a larger, randomized trial, the results are promising and indicate CMV may be a useful target for GBM therapy.

Molecular Profiling of T-cell Therapy Might Provide Prognostic Signatures

Predicting response to treatment or identification of markers that influence treatment efficacy could be highly beneficial for the clinical management of patients. To identify such prognostic signatures, we performed a comprehensive immunological and molecular profiling of antigen-specific T cells isolated from GBM patients. Gene expression analysis of the T-cell product used for infusion detected major changes compared with ex vivo T cells that were consistent with a signature of activation. Further
in-depth analysis revealed a signature of 7 genes that distinguished long-term disease free survivors from patients that relapsed more rapidly (Fig. 1). These genes were associated with T-cell effector function, potentially indicating that a more functionally active T-cell product is more effective in controlling cancer recurrence. Albeit preliminary, these results indicate prognostic biomarkers might be found by molecular analysis of T cells used for immunotherapy. Immunological and molecular analysis of peripheral blood T cells before and after immunotherapy failed to reveal any major changes that could have been indicative of response to treatment. Interestingly, tumor-infiltrating lymphocytes (TILs) isolated from a patient who relapsed after completing 4 T-cell infusions, displayed a distinct phenotype compared with T cells derived from peripheral blood of the same donor. This phenotype was consistent with local immunosuppression in the tumor which might contribute to treatment failure. This finding suggests that immunological profiling of lymphocytes in the tumor microenvironment could be an important tool to predict response to treatment and patient prognosis.

In summary, we have completed the first clinical assessment of CMV-specific adoptive immunotherapy for recurrent GBM. Autologous T-cell therapy was completely safe and coincided with extended progression free survival in 4 out of 10 patients. This study provides an important platform for further evaluation of cellular immunotherapy in the GBM setting, potentially in combination with other therapeutics.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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