Introduction

Brain tumors account for 1.4% of all cancers. 2) Glioblastoma is the most common primary brain tumor and accounts for approximately 40% of all primary brain tumors. These tumors are highly invasive, very aggressive, and often infiltrate eloquent areas within the brain. Due to the highly aggressive property acquired by genetic mutations, average survival of glioblastoma patients is no more than 12–18 months. The current treatment modality for glioblastoma includes surgical debulking of the tumor mass, biopsy, chemotherapy, and radiotherapy. Unfortunately, it is impossible to remove the entire tumor mass, resulting in the recurrences by remnants. Furthermore, increasing dose of chemotoxin and radiation will make normal tissue damage or necrosis. In spite of efforts and advances with these treatments, the mean survival time remained unchanged during the last few decades. Thus, additional therapies, such as immunotherapy, are needed to improve the survival time and the quality of life (QOL) for patients diagnosed with glioblastoma.

There is accumulating evidence to suggest that glioblastoma may be amenable to immune therapy approaches. Traditionally, brain has been regarded as immunologically privileged site, but several reports show that patients with glioblastoma can spontaneously develop antitumoral activity. Evidence suggests that microglial cells in brain act as antigen presentation cells (APC). However, patients with glioblastoma
have been characterized as immunodeficiency state of which the lymphocytes respond poorly to T cell mitogen or antigens. A number of immunosuppressive factors have been reported, to be involved in down-regulation of the cellular immune response in glioblastoma.

The local secretion of the transforming growth factor-β2 (TGF-β2) and interleukin-10 (IL-10) resulted in poor activation of the CD4+ subset and disruption of CD4+ : CD8+ T cell ratio. Recent reports demonstrate that the impaired CD4+ functions are related to an increase of CD4+ CD25+ regulatory T cell population and they play a key role in suppressing the response of the immune system against the tumors. Prostaglandin E2 (PGE2) is another factor secreted by infiltrating macrophage and is a key inducer of arginase, which will induce anergy of T cells. Also, these monocytes have decreased major histocompatibility (MHC) class II expression on their surface, preventing the recognition of tumor cells by T cells.

Due to these characteristics, efforts to improve efficacy of immunotherapy for glioblastoma are being directed at enhancing immunogenicity of glioma cells and cytotoxic activity of immune effector cells by administrating sensitized immune cells, administrating cytokines, or vaccinating with immune cells. These immunotherapies can be randomly categorized into three groups: 1) adoptive immunotherapy transplanting sensitized immune cells, 2) active immunotherapy promoting tumor specific cell-mediated immunity and 3) cytokine-mediated immunotherapy administrating immunostimulatory chemokines intravenously or intratumorally.

In this review, we will focus on the cell mediated immunotherapy against glioblastoma with particular emphasis on introduction of immunotherapy with cytokine-induced killer (CIK) cells.

1. Cytokine-mediated therapy

Since discovery of cytokines that stimulate both humoral and cellular immune responses as well as the activation of phagocytic cells, the therapeutic application of cytokines has been suggested. Most cytokines are thought to be able to enhance the efficiency of immune surveillance and induce immune-mediated tumor cell elimination. The fact that various cytokine receptors are expressed on the human glioma cell suggests potential means for immunotherapy against glioblastoma. With particular regard to glioma, several studies have used cytokines such as IL-2, IL-4, IFN-γ and IL-12 to promote the antitumoral activity of T cells or to enhance the immunogenicity.

Early trials utilizing systematic recombinant cytokines revealed the limitations of cytokine treatment in human cancers because of the toxicity or the short half-life of cytokines although they are able to stimulate strong tumoricidal responses. Given these limitations, strategies to overcome these concerns were attempted by using engineered cells, which is technique that makes cell secrete relevant cytokines. Several group described successful preclinical studies by administrating engineered cell lines secreting cytokine such as IL-2 and IL-4 into rodent model. Recently, gene transfer method using attenuated viral vectors has been also used and this approach generated encouraging results due to advantage of efficient infection of high virus titer and cytokine secretion by tumor tissue. Taken together, these data suggest that the application of cytokines in glioblastoma patients might be a useful adjunct for the immunotherapy.

2. Dendritic cells (DC)

Active immunotherapy strategies using dendritic cells (DC) vaccination are designed to elicit against glioblastoma. They require antigens such as synthetic peptides, tumor lysates, fused dendritic cells, and tumor cells for stimulating DC. In the past decades, significant progress has been made towards identification of glioma-associated proteins such as EphA2 or SOX11. However, there are some limiting factors for antigen-promoting DC therapy. These MHC class-I-restricted peptides activate CD8+ cells but not CD4+ T cells and it is difficult to identify any glioblastoma specific, immunogenically relevant tumor antigens. To bypass the step identifying relevant tumor antigens, it is useful to load dendritic cells with tumor lysates. In several clinical trials, it has been demonstrated that tumor lysates based DC vaccination is safe and feasible. A recent phase I clinical trial reported six of 10 patients showed robust systemic cytotoxicity after tumor lysate loaded DC vaccination and a significant CD8+ T cell infiltration was observed intratumorally in three of six patients who underwent reoperation. The median survival for patients with recurrent glioblastoma was 133 weeks, indicating that DC vaccination may confer some survival benefit. However, DC vaccination with tumor lysates requires surgical resection for obtaining substantial quantity of tumor lysates to serve as an antigenic source for DC priming. Therefore, DC vaccination with tumor lysates has the limitation regards to the patients with surgically inaccessible brain tumors.

Another part of strategy developed is to fuse tumor cells