Passive Immunotherapeutic Strategies for the Treatment of Malignant Gliomas

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KEYWORDS

• Malignant gliomas • Glioblastoma multiforme • Passive immunotherapy • Cellular therapy • Brain tumors

KEY POINTS

- Glioblastoma multiforme has a proclivity for widespread invasion and destruction of healthy parenchyma, displaying a poor outcome despite aggressive conventional treatment.
- Immunotherapy offers the potential to selectively target tumor cells, thereby decreasing collateral damage to normal brain.
- Passive immunotherapy includes administration of monoclonal antibodies and the adoptive transfer of lymphocyte-activated killer cells or cytotoxic T lymphocytes.
- Although many clinical trials have demonstrated promising results, further prospective randomized studies will be necessary to validate the effects of various passive immunotherapeutic approaches.

Malignant gliomas are the most common primary intracranial tumor, with a proclivity for widespread invasion and rampant destruction of healthy parenchyma. This infiltrative process affords high-grade gliomas protection from traditional therapies and subjects the adjacent normal tissue to potential damage from nonspecific treatment modalities.[1,2] Immunotherapies involving antibodies or sensitized effector cells can offer selective targeting of protein-carbohydrate complexes on tumor cell surfaces that distinguish neoplastic from noncancerous cells.[1,3] Consequently, the treatment of malignant gliomas may be enhanced not only by increased specificity for tumor tissue but also from decreased toxicity to the host's healthy cells.[1] This review focuses on published findings from the use of passive immunotherapy for the treatment of high-grade gliomas, particularly glioblastoma multiforme (GBM).

PASSIVE IMMUNOTHERAPY

Passive immunotherapy can be broadly categorized into 2 treatment approaches: one that relies on the administration of antibodies that may

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further be coupled to a toxic counterpart molecule or one involving the adoptive transfer of an activated immune cell effector component to act against a neoplasm in the host. For cellular therapy, the most common types have included the adoptive transfer of nonspecifically activated lymphocyte-activated killer (LAK) cells or specifically sensitized cytotoxic T lymphocytes (CTLs).[4,5] In adoptive immunotherapy (AIT), patients' native immune cells are extracted and then activated ex vivo to increase antitumor activity. These cells are then reinfused back into the patients either intravenously or directly placed into the tumor resection cavity. Another technique of passive immunotherapy involves monoclonal antibodies (mAbs). Antibody-mediated immunotherapy uses mAbs to induce lymphocyte recruitment and complement system activation, thereby resulting in tumor cytotoxicity. In addition, radiolabeled antibodies may deliver localized radiation to the target-specific neoplastic tissue, with subsequent induction of cell death.

AIT: LAK CELLS

LAK cells are nonspecific effector cells that are derived from peripheral blood mononuclear cells (PBMC) and activated ex vivo with high-concentration interleukin 2 (IL-2) (T-cell growth factor) to induce antitumor properties.[6–10] IL-2 is an endogenously produced cytokine that aids in the host's natural immune system and is available in recombinant form to facilitate LAK cell generation.[8–17] The LAK cell's cytolytic properties against numerous tumor types have been demonstrated in various models, with the enhanced capability of destroying natural killer (NK) cell–resistant malignant gliomas and sparing of normal parenchyma.[8,18–26] Furthermore, it has been suggested that the use of IL-2/LAK cell immunotherapy may possess preventative properties against metastasis and recurrence of disease because intraventricular administration can induce a systemic response.[8] Yet, given the high toxicity of intravenous IL-2, local administration of this cytokine has been adopted for an increased therapeutic response and decreased morbidity.[8,27–29] In addition, LAK cells are unable to migrate to tumor sites, necessitating local therapeutic administration at the surgical resection cavity.[30] However, LAK AIT has remained limited, in part, by the need for leukapheresis to obtain significantly therapeutic numbers of LAK cells, a costly process that may inhibit its use for many patients with GBM.

Nevertheless, 12 trials[8,25,26,29,31–38] including 211 patients (170 GBM) have been reported using LAK cell AIT for the treatment of recurrent high-grade gliomas. Although historically disappointing, more recent findings have demonstrated improvement in median survival for patients with GBM compared with control groups.[25]

In most studies, patients were included at the time of relapse and received 1 to 15 injections, containing 10^6 to 10^{10} injected LAK cells. Adverse effects included neurologic toxicity, cerebral edema, aseptic meningitis, and hypereosinophlia.[7,39] However, the local presence of eosinophils has been positively correlated with long-term survival and may be an indicator of treatment response.[8]

Efficacy was typically reported based on radiological criteria, demonstrating 5 complete responses (CR), 13 partial responses (PR), and 6 stable diseases (SD) in a total of 118 patients.[36] Of the data exclusive to 88 GBM patients, the investigators reported 3 CR (3.4%), 8 PR (11.0%), and 6 SD (6.8%). However, these figures do not include the beneficial results observed in the two most recent studies that included 73 patients with GBM.[25,31] In the most promising of studies, Dillman and colleagues[25] reported results of their phase II clinical trial demonstrating a 20.5-month median survival and 75% 1-year survival rate in 40 patients with GBM treated with intralesional autologous LAK cells; this has been the only report thus far investigating patients with newly diagnosed GBM treated with LAK cells. In addition, patients who received higher doses of CD3+/CD16+/CD56+ (T-NK) cells were found to have an increased survival advantage compared with those with lower T-NK cell counts that presumably resulted from steroid use during the month before leukapheresis. Given these findings, the investigators conducted a 2-arm, randomized phase II trial using either intralesional LAK cells or carmustine (Gliadel) wafers, following standard treatment with surgical resection and radio- and chemotherapy with temozolomide. Results of this study are currently pending publication.

Additionally, 3 other trials have also demonstrated improved median survival for patients with GBM compared with control groups. In a study preceding this last one, Dillman and colleagues[31] reported findings of 31 patients with recurrent GBM tumors, surviving a median time of 17.5 months from the date of the original diagnosis, compared with 13.6 months for a control group. Hayes and colleagues[33] reported results of 19 total patients with recurrent malignant gliomas, demonstrating a median survival for 15 cases of GBM of 53 weeks after reoperation versus 25.5 weeks for patients treated with conventional therapy alone. In a subsequent report, Hayes and colleagues[8] presented results of 15 patients with recurrent GBM (28 total cases of recurrent malignant gliomas)