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Clinical Study

A phase I/II clinical trial investigating the adverse and therapeutic effects of a postoperative autologous dendritic cell tumor vaccine in patients with malignant glioma

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ABSTRACT

Previous clinical trials of dendritic cell (DC)-based immunotherapy in patients with glioblastoma multiforme (GBM) have reported induction of systemic immune responses and prolonged survival. From 2003 to 2005, we performed a clinical trial in which patients with malignant glioma underwent surgery for maximal cytoreduction followed by a 6-month 10-injection course of autologous DC-tumor vaccine therapy, each injection containing 1–6 × 10^7 DC. Of the 17 treated patients (16 with World Health Organization grade IV and one with grade III glioma), eight (47.1%) had an initial transient elevation in aspartate aminotransferase (AST)/alanine aminotransferase (ALT). Vaccination caused some tumor shrinkage and increased concentration of tumor-infiltrating CD8(+) lymphocytes. Median survival and 5-year survival were 525 days and 18.8%, respectively, for 16 patients with grade IV glioma (381 days and 12.5% for eight newly diagnosed; 966 days and 25% for eight relapsed patients) compared to 380 days and 0% for 63 historical control patients. We concluded that autologous DC-tumor immunotherapy benefits patients with malignant glioma but may cause transient but reversible elevation of serum AST/ALT levels.

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1. Introduction

High grade gliomas are the most common malignant tumors of the central nervous system, with glioblastoma multiforme (GBM) being the most lethal. Despite advances in surgical as well as radiotherapeutic technologies and new chemotherapeutic agents, patients with malignant glioma continue to have a dismal prognosis. Prospective evaluation of a large cohort of patients has revealed that mean survival periods after diagnosis of World Health Organization (WHO) grade III and grade IV gliomas are 87 weeks and 45 weeks, respectively.[1]

Recently, cancer immunotherapy has been pursued by exploitation of dendritic cells (DC), "professional" antigen processing and presenting cells, to induce specific anti-tumor responses.[2,3] It is now known that injection of mature DC boosts a superior CD8(+) T-cell immune response.[4] Ideally, injected DC must migrate to the T-cell area of local lymph nodes for antigen presentation.[5] Several clinical trials of autologous DC-based vaccine therapy in malignant gliomas[6–13] have reported the induction of glioma-specific anti-tumor immune responses and apparent survival benefits for some patients. Based on several years of translational research on autologous DC-tumor vaccine therapy, in 2003–2005 we performed a clinical trial mainly of WHO grade IV glioma to assess adverse effects and 5-year patient survival benefits of our modified DC vaccine preparations at relatively large doses. This report was written according to the current CONSORT statement of non-pharmacologic treatment.[14]

2. Materials and methods

2.1. Protocol

This open-labeled, single-arm clinical trial, titled "Dendritic Cell-based Adjuvant Immunotherapy of Malignant Brain Gliomas" (Notice of Approval – EY-DOH-MD #0910072504, December 2002), was performed according to the Guidelines of Somatic Cell Therapy for Human Clinical Trials (http://www.doh.gov.tw). The protocol was endorsed by the Institutional Review Board of Chang

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Gung Memorial Hospital (CGMH) after peer review and was then subjected to independent expert review for official approval by the Department of Health in Taiwan. Patients with WHO grade III or IV glioma who met the inclusion criteria were enrolled after providing signed informed consent. Patients received apheresis to obtain peripheral blood mononuclear cells, either before or after craniotomy for maximal cytoreduction. We grew glioma cells from the surgical specimen and derived the phagocytic DC from peripheral blood monocytes to prepare an individual batch of autologous DC-tumor vaccine for every participating patient. We provided each patient with a booklet that described the trial in lay Chinese and an individualized treatment plan with scheduled dates of surgery/radiotherapy (new patients), vaccine therapy and follow-up visits for medical/neurological examinations, MRI and laboratory tests.

2.2. Patient enrollment

We enrolled male and female patients with the following inclusion criteria: new or recurrent WHO grade III or IV glioma; Karnofsky performance scale (KPS) score $\geqslant 70$; age 17–70 years; absence of human immunodeficiency virus infection, active viral hepatitis, syphilis, rheumatic disease, other malignancy, or autoimmune disease; not pregnant or breast feeding; without high dose corticosteroid treatment (dexamethasone 20 mg/day); within the normal ranges for hemoglobin, granulocytes, platelets, prothrombin time (PT), activated partial thromboplastin time (APTT), creatinine, blood urea nitrogen, aspartate aminotransferase (AST), alanine aminotransferase (ALT); and suitability or willingness to receive pre-vaccination maximal surgical cytoreduction at CGMH.

2.3. Surgical and radiation treatment

Craniotomy for maximal cytoreduction was performed first. The patients newly diagnosed with GBM received standard, post-surgical 60 Gy external radiation therapy before vaccination. For patients with relapsed tumors, craniotomy was performed without subsequent radiotherapy.

2.4. Vaccine preparation

One of us (DMY) performed all DC vaccine preparation procedures within a high efficiency particle arrestance (HEPA)-filter clean-air barrier "Good Laboratory Practice" (GLP) facility in Academia Sinica (Taipei). Within 3 hours of surgery, tumor specimens were rinsed, finely minced and collagenase-digested to disaggregate the tumor cells; single cells and tiny tumor fragments were collected by centrifugation and used for short-term glioma cell cultures, as described previously.[15] For vaccine preparation, glioma cells were grown to 10^8 in number, which usually took 4–5 passages.

We derived phagocytic DC from peripheral blood monocytes, as reported previously.[16–18] Briefly, 10^9–10^{10} peripheral blood mononuclear cells were collected by apheresis; isolated monocytes stimulated with human recombinant granulocyte-macrophage colony stimulating factor (Immunex, Amgen, Thousand Oaks, CA, USA) and interleukin-4 (R&D Systems, Minneapolis, MN, USA), both 50 ng/mL, in serum-free AIM-V® medium (Gibco Invitrogen, Carlsbad, CA, USA) for 6 days. The phagocyte differentiation of DC was assessed by cytofluorometric assay of tartrate-resistant acid phosphatase.[19] To the phagocytic DC, we added equal numbers of autologous glioma cells that had been immunogenically enhanced by interferon-gamma and heat-shock treatment[20] and then irradiated with 100 Gy in a cesium source. The cell mixture was co-cultured for 24 hours, collected by centrifugation and cryopreserved in 12 aliquots, as an individual vaccine lot for each patient, in a liquid nitrogen freezer.

2.5. Intervention and vaccine administration protocol

In newly diagnosed patients we initiated vaccine therapy after completion of post-surgical radiotherapy, whereas in patients with relapsed tumor, vaccine therapy started directly upon recovery from craniotomy. The vaccination protocol for this 6-month, 10-injection course was: every week, 4 times; followed by every 2 weeks, twice; and then every month, 4 times. For each injection, one aliquot of the vaccine lot was thawed rapidly, washed in clinical grade normal saline and incubated in a DC maturation medium at 37 °C for 3 hours. The matured DC tumor vaccine was injected subcutaneously over lymph nodes of either axilla. The injection schedule was interrupted in patients who received craniotomies for recurrent tumors or withdrew voluntarily from the trial.

2.6. Clinical parameters of outcomes

The first two patients were hospitalized for 3 days for their first vaccine injection. As no acute adverse effects were evident, all subsequent vaccine injections were administered at the outpatient clinic. The National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0, including allergy, constitutional symptoms, skin reaction, infection, and metabolic, neurological, pain, and renal symptoms, were followed to assess the adverse effects weekly for the first 2 months, then monthly for the remaining months. We performed MRI before and after craniotomy to determine the extent of tumor resection, then every 2 months during the vaccination period. Progressive tumor recurrence or any associated morbidities were treated accordingly, including repeat craniotomies. Each patient was followed regularly throughout the survival period or for more than 5 years.

2.7. Pathology and immunohistochemical analysis

Surgical specimens were assessed by Dr. S.M. Jung, neuropathologist at CGMH, using the WHO criteria of grade III and IV gliomas. To assess glioma cell differentiation and tumor infiltrating T-lymphocytes, paraffin-embedded sections of the surgical tumor specimens were also stained with antibodies to p53, glial fibrillary acidic protein, nestin, CD3, CD4, and CD8, and examined by optical as well as fluorescent microscopy (Zeiss Axiophot 2 fluorescence microscope; Zeiss, Oberkochen, Germany).

2.8. Historical control

Of more than 200 patients with GBM or grade IV glioma who received the standard surgical and radiotherapy procedures at CGMH from 1995 to 2002, 63 had also been diagnosed by Dr. S.M. Jung, and hence served as grade IV historical control patients. These patients were sex-matched and age-matched with the 16 patients with grade IV glioma in this clinical trial.

2.9. Statistical analysis

To determine the factors that might affect the survival benefit of the vaccine treatment, univariate analysis was performed by Fisher's exact test, the Wilcoxon log-rank test, and Cox regression modeling to account for age, sex, diagnosis (new *versus* recurrent), adverse effects (lymphopenia and elevated serum ALT/AST concentrations), post-surgical KPS score, MRI showing recurring tumors, and presence or absence of signs of disease progression, which were all assessed using clinical and laboratory data collected at various periods of the clinical trial.

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