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Safety evaluation of high-dose BCNU-loaded biodegradable implants in Chinese patients with recurrent malignant gliomas

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ABSTRACT

Objectives: Malignant gliomas are common primary brain tumors with dismal prognosis. The blood–brain barrier and unacceptable systemic toxicity limit the employment of chemotherapeutic agents. BCNU-impregnated biodegradable polymers (Gliadel®) have been demonstrated to prolong the survival of patients with malignant gliomas. Until now, no biodegradable drug delivery system has been commercially available in China. In the present study, we evaluated the safety of implants with high-dose BCNU in Chinese patients with recurrent malignant gliomas.

Patients and methods: Adults with supratentorial recurrent malignant glioma were eligible. High-dose BCNU-loaded PLGA implants (20 mg of BCNU in each implant) were placed in the debulking cavity. The implants were investigated by a classical 3 + 3 design. Four levels of BCNU, up to 12 implants, were evaluated. Pharmacokinetic sampling was performed. The toxicity of the implants and the survival of patients were recorded.

Results: Fifteen recurrent patients were enrolled with 12 glioblastomas and 3 anaplastic gliomas. Among 15 patients, 3 were treated with 3 implants (60 mg of BCNU), 3 with 6 implants (120 mg), 3 with 9 implants (180 mg) and 6 with 12 implants (240 mg). No dose-limiting toxicity was observed in the cohort of patients. Subgaleal effusion was the most common adverse event, presenting in 7 patients (46.7%). The median overall survival (OS) was 322 days (95% CI, 173–471 days). The 6-month, 1-year and 2-year survival rates were 66.7%, 40% and 13.3%, respectively.

Conclusions: The high-dose BCNU-loaded PLGA implants were safe for Chinese patients with recurrent malignant gliomas and further investigation for efficacy is warranted.

1. Introduction

Malignant gliomas compose the majority of primary malignant tumors in the central nervous system (CNS), but patient prognosis is far from satisfactory. The blood–brain barrier (BBB) hampers the permeability into the CNS of many active chemotherapeutic agents; thus, systemic administration of cytotoxic or targeting drugs must consider BBB effects on drug delivery. Interstitial chemotherapy is a promising strategy for malignant gliomas because the direct delivery of chemotherapeutic agents into the tumor bed bypasses the BBB and also reduces systemic toxicity. Chemotherapeutic delivery through Gliadel® wafers, which each contains 7.7 mg of 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU) embedded in Polifeprosan 20, is currently the most successful biodegradable local delivery system for gliomas. Clinical trials

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and systematic reviews have demonstrated that Gliadel® wafers are safe and effective in the treatment of malignant gliomas; the US national comprehensive cancer network (NCCN) recommendations include carmustine (BCNU) wafers in guidelines for both newly diagnosed and recurrent anaplastic gliomas and glioblastoma multiforme (GBM) [1–3]. To date, biodegradable polymers that deliver chemotherapeutic agents for malignant gliomas have not been commercially available in China. In this study, we evaluated the safety of high-dose BCNU-loaded implants to treat Chinese patients with recurrent malignant gliomas.

2. Patients and methods

2.1. Patients

This was a phase I single-arm trial. Adult patients aged from 18 to 65 years, with surgical indication for radiologically suspect recurrent superatentorial malignant glioma, were initially selected for enrollment screening. Patients with a history of histologically confirmed malignant glioma were eligible. If a patient had a history of low-grade glioma, the intraoperative frozen section diagnosis of malignant glioma was required for eligibility in the current study. Malignant glioma in this study encompassed anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic oligoastrocytoma (AOA) and GBM. Additional inclusion criteria included Karnofsky performance status (KPS) $\geq$60; four or more weeks since their last chemotherapy (>6 weeks for nitrosoureas); hemoglobin $\geq$90 g/L; absolute neurophil count (ANC) $\geq 1.5 \times 10^9$/L; platelet count $\geq 100 \times 10^9$/L; aspartate aminotransferase (AST) and alanine aminotransferase $\leq$2.5 times upper limit of normal (ULN); serum bilirubin and creatinine $\leq$1.5 times ULN. Excluded were patients with multifocal tumor, known hypersensitivity to nitrosoureas and/or poly (lactide-co-glycolide) (PLGA), prior interstitial radiotherapy or chemotherapy, significant laboratory abnormalities, 3 or more tonic-clonic seizures in a month, and/or the communication between the surgical resection cavity and the ventricular system. The study protocol was approved by the State Food and Drug Administration (SFDA) of China and the ethics committee at Sun Yat-sen University Cancer Center. Written informed consent was obtained from all the patients.

2.2. BCNU-loaded PLGA implants

BCNU-loaded PLGA implants employed in the current study were developed and supplied by Lanjin Pharmaceutical Co. (Jinan, China). The BCNU-loaded PLGA implant is a pale yellow disk with a diameter of 14 mm and a thickness of 1 mm (Fig. 1A), stored at 2–10 °C. The matrix of the implants is a copolymer of lactide and glycolide in a 50:50 ratio. Ten percent of BCNU loading achieved 20 mg of BCNU per implant.

2.3. Neurosurgical procedure and management after implantation

The procedure for BCNU-loaded PLGA implant was similar to that for Gliadel® wafers described by Brem et al. [4] Briefly, implants were placed on the surface of resection cavity after removal of the tumor. Overlapping of implants was permitted. Sheets of oxidized regenerated cellulose (Surgicel) or absorbable gelatin sponge were occasionally

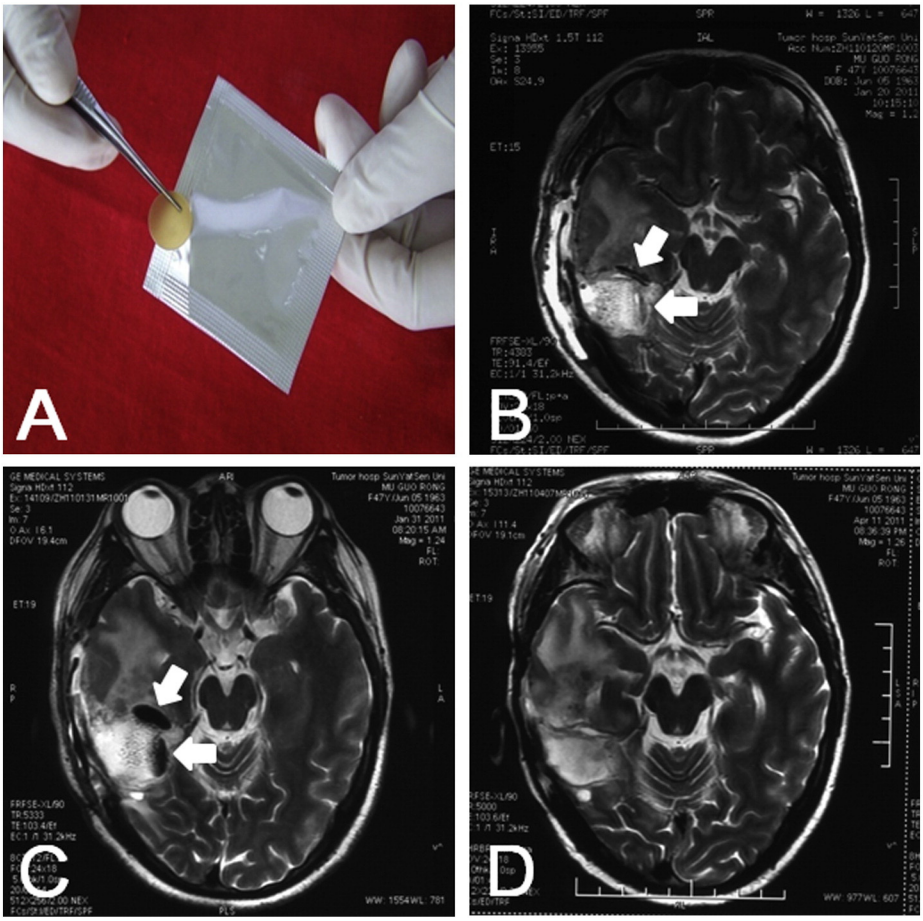

Fig. 1. Physical and imaging characteristics of BCNU-loaded PLGA implants. The BCNU-loaded PLGA implant is a pale yellow disk, with a diameter of 14 mm and a thickness of 1 mm (A). The implants presented as hypointense objects on T2-weighted MR images (Day 3 after implantation, arrows in B). The volume of the implants expanded gradually (Day 14 after implantation, arrows in C). The implants were undetectable on MRI 3 months after implantation (D).