Journal of Cancer Research and Practice 3 (2016) 63–68

Contents lists available at ScienceDirect

Journal of Cancer Research and Practice

journal homepage: http://www.journals.elsevier.com/journal-of-cancer-research-and-practice

Review article

Non-invasive focused ultrasound-based synergistic treatment of brain tumors

Ya-Jui Lin, Ko-Ting Chen, Chiung-Yin Huang, Kuo-Chen Wei*

Department of Neurosurgery, Linkou Chang Gung Memorial Hospital, School of Medicine, Chang Gung University, Taoyuan, Taiwan

ARTICLE INFO

Article history:
Received 27 July 2015
Accepted 4 January 2016
Available online 8 June 2016

Keywords:
Focused ultrasound
Blood–brain barrier
Brain tumor
Nanocarrier
Neuronavigation

ABSTRACT

Among the primary brain tumors, gliomas are the most commonly found. In the United States, these tumors account for approximately 78% of the new cases of primary malignant brain and central nervous system (CNS) tumors diagnosed annually. Glioblastoma multiforme (GBM) is the most common and aggressive type of glioma, with the poorest survival duration. Although surgical techniques, radiotherapy and chemotherapy have improved, the prognoses of patients with glioblastomas are still poor (~1 year), which is largely because of the spread of tumor cells to other regions of the brain. Intravenous administration of chemotherapy drugs is the standard procedure for treat these spreaded cells, but the treatment effect is limited because of the adverse side effect and the delivery blockage from the blood–brain barrier (BBB). Thus, developing an effective treatment system to conquer this blockage will be beneficial for those who suffer from malignant brain tumor.

Focused ultrasound (FUS) sonication in the presence of microbubbles (MB) may be able to promote the effectiveness of drug delivery, and help to overcome the blockage. The oscillation and destruction of microbubbles as well as microstreaming and radiation forces are the key factors capable of creating the transient rupture of the vascular barriers and subsequent increase in the tumor's vascular permeability.

The success of FUS BBB disruption in delivering a variety of therapeutic molecules into brain tumors has recently been demonstrated in an animal model. In this paper the authors review a number of critical studies that have demonstrated successful outcomes, including enhancement of the delivery of traditional clinically used chemotherapeutic agents or application of novel nanocarrier designs for actively transporting drugs, or extending drug half-lives to significantly improve treatment efficacy in preclinical animal models.

1. Introduction

Gliomas are the most common of the primary brain tumors; in the United States, they account for approximately 78% of the new cases of primary malignant brain and central nervous system (CNS) tumors diagnosed annually. Glioblastoma multiforme (GBM) is the most common and aggressive glioma, with the poorest survival. It is a highly malignant brain tumor, typically affecting adults between 45 and 60 years of age. Although surgical techniques, radiotherapy and chemotherapy have improved, the prognoses of patients with glioblastomas are still poor, largely because of the spread of tumor cells to other regions of the brain.

The chemotherapeutic agent 1,3-bis- (2-chloroethyl)- 1-nitrosourea (BCNU, also known as carmustine) and Temozolomide (TMZ), have become commercially available to be used in the treatment of malignant brain tumors. Although it improves patient survival, its efficiency is limited by side effects such as myelosuppression, hepatic toxicity, and pulmonary fibrosis, which increases the difficulty of clinical treatment. The effect is limited because of adverse side effect and delivery blockage from the blood–brain barrier (BBB). The BBB is composed of endothelial cell tight junctions (zonulae occludens), basal lamina and glial processes. In addition, endothelial cells of cerebral vessels are devoid of fenestrations and transendothelial channels, and have a paucity of pinocytotic vessels. Thus, the BBB plays a protective role in the central nervous system (CNS), restricting the movement of many substances into the brain. Thus, developing a new brain tumor

* Corresponding author. Department of Neurosurgery, Linkou Chang Gung Memorial Hospital, No. 5, Fu Xing St., Gueishan, Taoyuan, 333, Taiwan.
E-mail address: kuochenwei@cgmh.org.tw (K.-C. Wei).
Peer review under responsibility of The Chinese Oncology Society.

http://dx.doi.org/10.1016/j.jcrpr.2016.05.001

therapeutic system precisely targeting the tumor cells is urgently needed.

Focused ultrasound (FUS) sonication in the presence of microbubbles (MB) can disrupt the BBB, increasing its permeability.[1] This type of disruption is transient and reversible, and does not damage neural cells. The oscillation and destruction of microbubbles as well as microstreaming and radiation forces are the key factors possible to create the transient rupture of vascular barriers and subsequent increase in the tumor's vascular permeability. This method could provide a means for targeted delivery of therapeutic or diagnostic agents to the brain.

2. Focused ultrasound with chemotherapeutic agent

2.1. BCNU

In our hypothesis, transcranial focused ultrasound in the presence of microbubbles disrupted the BBB and then enhanced drug delivery. Therefore, we implanted the cultured glioma cells in rat brain as the tumor model. BCNU (13.5 mg/kg) was administered intravenously. MR imaging was used to evaluate the effect of treatments, including analysis of tumor progression and animal survival, and brain tissues were histologically examined.[1,2]

The concentration of BCNU through the BBB was enhanced both in normal brains (by 340%) and tumor-implanted brains (by 202%) without intracranial hemorrhage (Fig. 1). In addition, treatment of tumor-implanted rats with focused ultra-sound alone had no beneficial effect on tumor progression.

Administration of BCNU only transiently controlled tumor progression. Nevertheless, relative to untreated controls, the duration of animal survival was improved by treatment with BCNU alone (increase in median survival time, 15.7%, $P = .023$). Treatment with focused ultrasound before BCNU administration controlled tumor progression and improved animal survival relative to untreated controls (increase in median survival time, 85.9%, $P = .0015$).[1] These results revealed disruption of the BBB by using focused ultrasound, which significantly enhances the penetration of BCNU through the barrier. Furthermore, treatment of tumor-implanted rats with focused ultrasound before administration of BCNU both controlled tumor progression and improved animal survival.[1,2]

2.2. Temozolomide (TMZ)

Temozolomide (TMZ) is the most important chemotherapy agent administered to control glioma progression. It is an alkylating agent of the imidazotetrazine series that possesses strong antineoplastic activity against high-grade glioma.[3,4] TMZ is an oral

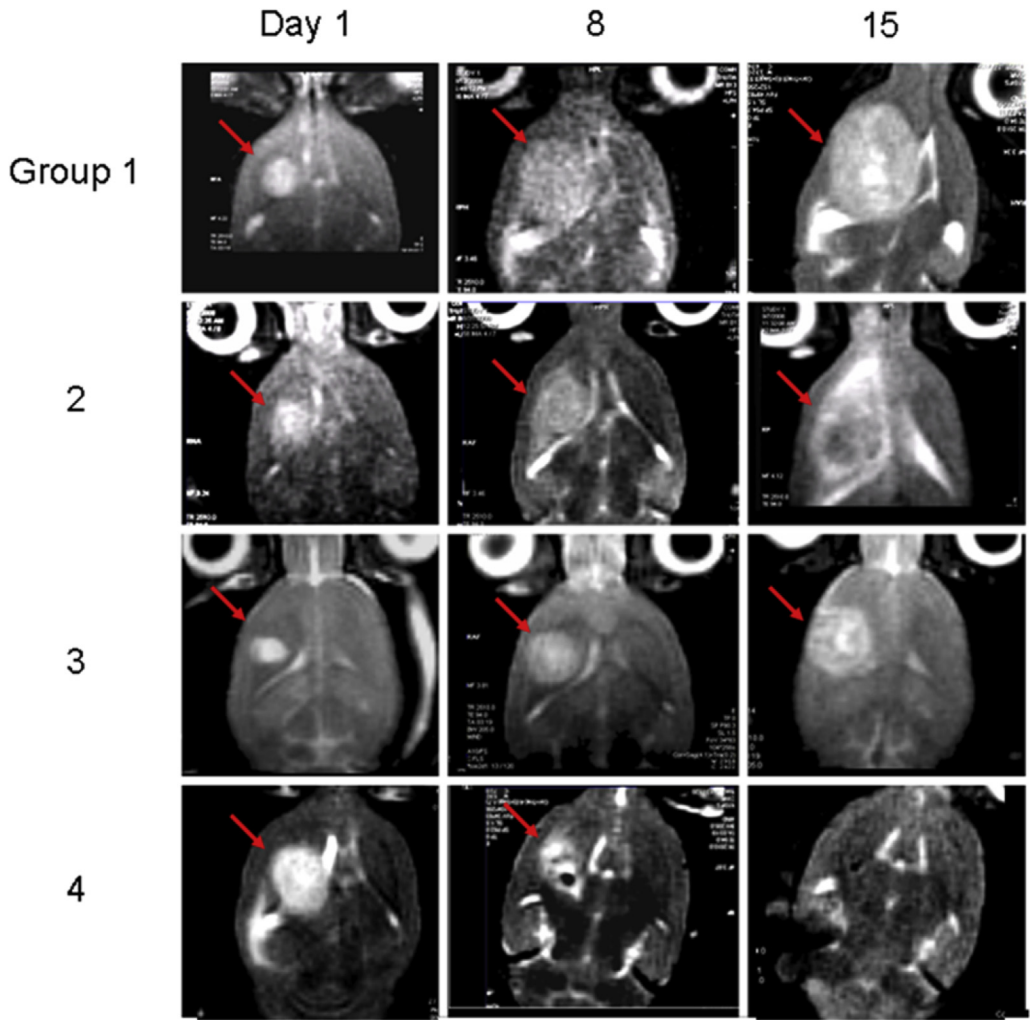

Fig. 1. Treatment effect of FUS-enhanced BCNU in brain tumor bearing rats. Group 1: control group; group 2: rats treated with ultrasound only; group 3: rats treated with BCNU only; group 4: rats treated with BCNU enhanced by FUS.