Neurochemical Research
https://doi.org/10.1007/s11064-019-02795-4

ORIGINAL PAPER

Provocative Question: Should Ketogenic Metabolic Therapy Become the Standard of Care for Glioblastoma?

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Received: 22 January 2019 / Revised: 3 April 2019 / Accepted: 4 April 2019

Abstract

No major advances have been made in improving overall survival for glioblastoma (GBM) in almost 100 years. The current standard of care (SOC) for GBM involves immediate surgical resection followed by radiotherapy with concomitant temozolomide chemotherapy. Corticosteroid (dexamethasone) is often prescribed to GBM patients to reduce tumor edema and inflammation. The SOC disrupts the glutamate–glutamine cycle thus increasing availability of glucose and glutamine in the tumor microenvironment. Glucose and glutamine are the prime fermentable fuels that underlie therapy resistance and drive GBM growth through substrate level phosphorylation in the cytoplasm and the mitochondria, respectively. Emerging evidence indicates that ketogenic metabolic therapy (KMT) can reduce glucose availability while elevating ketone bodies that are neuroprotective and non-fermentable. Information is presented from preclinical and case report studies showing how KMT could target tumor cells without causing neurochemical damage thus improving progression free and overall survival for patients with GBM.

Keywords Ketogenic diet · Glucose · Glutamine · Glutamate · Warburg · Substrate level phosphorylation · Fermentation

Abbreviations

GBM Glioblastoma
TMZ Temozolomide
SOC Standard of care
KMT Ketogenic metabolic therapy

Special issue in honour of Professor Vera Adam-Vizi.

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Introduction

Glioblastoma (GBM) remains largely unmanageable and has among the highest mortality rates for primary brain tumors. Median life expectancy following diagnosis is only about 11–14 months for most GBM patients regardless of the hype surrounding some of the newer of therapies [1–5]. A recent reevaluation found that overall survival for GBM (8–14 months) is woefully similar to that reported by Bailey and Cushing almost a century ago [5, 6]. Indeed, US Senator, John McCain, was diagnosed with GBM in May 2017, and died in August 2018. The 'Secondary Structures of Scherer' are the defining characteristic of GBM, which include diffuse parenchymal invasion and growth over the subpial surface, along white matter tracks, and through the Virchow–Robin spaces [7–11]. The highly invasive nature of GBM through these secondary structures makes most current therapies ineffective [12–15]. The quality of life has also remained poor for most GBM patients especially for those receiving radiation and the toxic alkylating agent, temozolomide [16–18] (Fig. 1).

GBM contains a range of morphologically diverse neoplastic cell types that express neural, glial, and myeloid/mesenchymal markers [3, 19–27]. Also recognized are

Published online: 25 April 2019