Critical Reviews in Oncology/Hematology 112 (2017) 41–58

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Role of ketogenic metabolic therapy in malignant glioma: A systematic review

Sebastian F. Winter[a,b], Franziska Loebel[b,c], Jorg Dietrich[a,d,*]

[a] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA
[b] Faculty of Medicine, Charité – University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany
[c] Department of Neurosurgery, Charité – University Medicine Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
[d] MGH Cancer Center and Center for Regenerative Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Yawkey 9E, Boston, MA 02114, USA

Contents

1. Introduction 42
   1.1. Current treatment of malignant glioma: concerns and boundaries 42
   1.2. Understanding brain cancer as a metabolic disease 42
   1.3. A role for ketogenic metabolic therapy in malignant glioma? 42
2. Materials and methods 43
3. Results 43
   3.1. Ketogenic metabolic therapy in brain cancer: preclinical evidence and putative mechanisms 43
   3.2. Therapeutic value of ketogenic metabolic therapy in malignant glioma treatment 46
      3.2.1. Published clinical data 46
      3.2.2. Ongoing clinical trials 49
4. Discussion 53
   4.1. Future directions to advance KMT in neuro-oncology 53
5. Conclusions 55
   Conflicts of interest 55
   Acknowledgements 55
   Appendix A. Supplementary data 55
   References 55

ARTICLE INFO

Article history:
Received 1 October 2016
Received in revised form 30 January 2017
Accepted 14 February 2017

Keywords:
Malignant glioma
Glioblastoma multiforme
Cancer metabolism
Ketogenic diet
Low glycemic diet
Metabolic therapy
Adjunctive cancer therapy

ABSTRACT

Background: Coined as the "Warburg effect" and a recognized hallmark of cancer, energy metabolism is aberrantly geared towards aerobic glycolysis in most human cancers, including malignant glioma. Ketogenic metabolic therapy (KMT), i.e. nutritional intervention with ketogenic or low-glycemic diets, has been proposed as an anti-neoplastic strategy in glioma patients.
Materials and methods: We here review the rationale and existing data investigating KMT in management of patients with malignant glioma and discuss the promise and potential challenges of this novel strategy. Results from published clinical studies and ongoing clinical trials on the topic are systematically reviewed, including 6 published original articles and 10 ongoing clinical trials. Search criteria for this review entailed the databases MEDLINE, EMBASE, Cochrane CENTRAL, and Google Scholar, as well as ICTRP (WHO) and ClinicalTrials.gov (NIH) registries.
Results: A substantial amount of preclinical literature demonstrates KMT efficacy and safety in model systems of malignant glioma. Clinical literature indicates KMT safety and feasibility; 2 clinical studies suggest KMT-associated anti-neoplastic efficacy and clinical benefit. Ongoing clinical trials address KMT safety and metabolic impact, patient compliance, and patient clinical/survival benefit.

* Corresponding author at: Massachusetts General Hospital Cancer Center, 55 Fruit Street, Yawkey 9E, Boston, MA 02114, USA.
E-mail addresses: sebastian-friedrich.winter@charite.de (S.F. Winter), franziska.loebel@charite.de (F. Loebel), Dietrich.Jorg@mgh.harvard.edu (J. Dietrich).

http://dx.doi.org/10.1016/j.critrevonc.2017.02.016

Conclusions: While clinical evidence is still limited in this evolving field, increasing numbers of ongoing clinical trials suggest that KMT is emerging as a potential therapeutic option and might be combinable with existing anti-neoplastic treatments for malignant glioma. Emerging clinical data will help answer questions concerning safety and efficacy of KMT, and are aiming to identify the most promising KMT regimen, compatibility with other anti-cancer treatments, ethical aspects, and impact on quality of life of cancer patients.

1. Introduction

Malignant glioma is the most common primary brain tumor (Ostrom et al., 2014; Crocetti et al., 2012). Glioblastoma multiforme (GBM), the most frequent and most aggressive type of glioma (Tanaka et al., 2013; Venur et al., 2015), carries an exceptionally poor prognosis. With a median overall survival (OS) between 12 and 15 months from time of diagnosis (Wen and Kesari, 2008; Carlsson et al., 2014) and a 5-year survival rate of less than 5% (Carlsson et al., 2014) despite maximal treatment, there is a pressing need to identify and implement more efficacious therapies.

1.1. Current treatment of malignant glioma: concerns and boundaries

The current standard of care (SOC) for glioblastoma patients consists of maximal safe resection, followed by radiotherapy and concurrent chemotherapy with Temozolomide (TMZ) (Venur et al., 2015; Alifieris and Trafalis, 2015; Anton et al., 2012). Tumor-associated symptoms arising from peritumoral edema are generally managed with glucocorticoids (Dietrich et al., 2011; Schiff et al., 2015; Roth et al., 2010). Anti-angiogenic treatment with bevacicumab (Avastin) has shown to provide some benefit on quality of life and progression-free survival (PFS), but not OS (Khasraw et al., 2014; Chinot et al., 2014; Gilbert et al., 2014). Despite substantial clinical research efforts over the past decades, therapeutic progress has been marginal (Frosina, 2015); added benefits from TMZ (Hart et al., 2013) and bevacizumab (Khasraw et al., 2014) are modest and patient OS remains poor. Apart from provoking classical side effects associated with anti-cancer therapy, the current SOC bears additional CNS-specific side effects, including cognitive decline and structural brain changes associated with chemotherapy and radiation (Prust et al., 2015; Kaiser et al., 2014; Monje and Dietrich, 2012; Dietrich et al., 2008; Dietrich, 2010). While putative genetic mutations and abnormal signaling pathways are implicated in disease pathogenesis (Tanaka et al., 2013; Bastien et al., 2015), GBMs are highly heterogeneous in nature (Aum et al., 2014; Prados et al., 2015), i.e. consisting of distinct cellular subpopulations with differing genetic mutations and gene expression profiles (Parsons et al., 2008; Brennan et al., 2013; Crespo et al., 2015). Tumor heterogeneity and rapidly evolving resistance mechanisms have been considered as likely reasons for the lack of durable responses with novel targeted therapies that usually rely on blocking specific signaling pathways.

1.2. Understanding brain cancer as a metabolic disease

A hallmark of cancer (Hanahan and Weinberg, 2011), tumor cell energy metabolism is usually aberrantly shifted towards “aerobic glycolysis” (Seyfried et al., 2014). Following glycolysis, pyruvate is fermented to lactate despite cellular availability of oxygen – a phenomenon coined as the “Warburg effect” following the discoveries of the German physician, biochemist, and Nobel laureate Otto Warburg nearly a century ago (Warburg and Posener, 1924; Warburg and Dickens, 1930). Malignant glioma cells critically depend on glucose as the main energy source to survive and sustain their aggressive properties (Jelluma et al., 2006). Like most cancers (Fulda et al., 2010), GBMs usually have dysregulated mitochondria, impeding efficient TCA cycle and oxidative phosphorylation activities necessary for aerobic ATP production (Seyfried et al., 2014; Seyfried et al., 2011). This is not only reflected by abnormal proteomic changes within the mitochondrial metabolic and apoptotic regulatory machinery (Deighton et al., 2014; Guntuku et al., 2016), but also by abundant ultrastructural mitochondrial pathology such as cristolysis and mitochondrial swelling found in human astrocytoma and GBM tumor cells (Deighton et al., 2014; Guntuku et al., 2016; Arismendi-Morillo and Castellano-Ramirez, 2008). Most tumor cells thus rely on generating ATP mainly through the comparatively inefficient cytosolic glycolysis pathway. In a compensatory manner, glycolytic gene expression and associated glycolytic rates are commonly upregulated in malignant glioma (Oudard et al., 1997; Oudard et al., 1996; Ru et al., 2013; Sanzey et al., 2015). Numerous preclinical studies have confirmed this compelling glucose-dependency (Seyfried et al., 2011; Seyfried et al., 2015; Varshneya et al., 2015; Woolf and Scheck, 2015), corroborated by clinical findings identifying hyperglycemia as a negative predictor of OS in GBM patients (Adeberg et al., 2015; Tieu et al., 2015; Mayer et al., 2014; Derr et al., 2009; McGirt et al., 2008; Liu et al., 2015).

1.3. A role for ketogenic metabolic therapy in malignant glioma?

Despite ample evidence of abnormally regulated energy metabolism in malignant glioma (Seyfried et al., 2011; Ru et al., 2013), nutritional strategies targeting glycemic modulation to exploit the observed tumor glucose-dependency have not yet been thoroughly investigated in clinical trials and existing clinical data is limited (Strowd and Grossman, 2015). Notably, it has been hypothesized that the current SOC, while evidently providing at least temporary modest benefit for symptomatic management and OS, might actually contribute to tumor progression in the long-term (Seyfried et al., 2011; Seyfried et al., 2015; Maroon et al., 2015). For instance, recent evidence suggests that TMZ might cause a hypermutational phenotype with concerns of increased tumor aggressiveness (Yip et al., 2009). Moreover, it has been speculated that tissue injury from surgery and standard cytotoxic treatment can promote persistent neuro-inflammation within the tumor microenvironment (Lee et al., 2010; Monje et al., 2007; Brandsma et al., 2008), potentially driving tumor progression (Kyritsis et al., 2011; Yeung et al., 2013). Beside these major concerns, standard treatments are usually non-specific resulting in collateral brain tissue damage while providing inflammation-induced proliferative and pro-angiogenic stimuli to tumor cells. Moreover, recent evidence suggests that glucocorticoids – administered to nearly all glioma patients throughout the course of their disease for edema-related symptom management (Chang et al., 2005) – in their immunosuppressive and anti-proliferative nature might actually interfere with cytotoxic treatment efficacy and diminish OS in patients with GBM (Wong et al., 2015; Pitter et al., 2016). Glucocorticoids also contribute to hyperglycemia (Harris et al., 2013;