Medical Hypotheses 118 (2018) 19–25

Contents lists available at ScienceDirect

Medical Hypotheses

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

A hypothetical method for controlling highly glycolytic cancers and metastases

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A B S T R A C T

Most proliferating cancer cells and cancer-associated tumor stroma have an upregulated glucose energy demand in relation to normal cells. Cancer cells are further less metabolically flexible than normal cells. They can therefore not survive metabolic stress as well as normal cells can. Metabolic deprivation thus provides a potential therapeutic window.

Unfortunately, current glucose blockers have toxicity problems. An alternative way to reduce a cancer patient's blood glucose (BG), for a short-term period to very low levels, without the concomitant toxicity, is hypothesized in this paper.

In vitro tests have shown that short-term BG deprivation to 2 mmol/L for 180 min is an effective cancer treatment. This level of hypoglycaemia can be maintained *in vivo* with a combination of very low-dose insulin and the suppression of the glucose counter-regulation system. Such suppression can be safely achieved by the infusion of somatostatin and a combination of both α and β-blockers.

The proposed short-term *in vivo* method, was shown to be non-toxic and safe for non-cancer patients. The next step is to test the effect of the proposed method on cancer patients. It is also suggested to incorporate well-known, long-term BG deprivation treatments to achieve maximum effect.

Background

Preamble

The majority of cancer-associated deaths are due to solid metastatic, mostly glucose-addicted cancers [1]. The high glucose uptake by many cancer cells compared to normal cells, creates a therapeutic window [2–6].

Metabolic deprivation treatment has a different effect on normal healthy cells than on malignant cells [6,7]. Normal cells have metabolic flexibility in order to survive under metabolic stress. Malignant cells on the other hand lack this flexibility, due to cumulative genetic mutations [8]. This difference can be exploited in cancer treatment.

The research group has therefore previously published work on metabolic strategies to treat highly glycolytic cancers and metastases (HGCM) via lifestyle interventions, drugs and/or haemodialysis [6,9,10]. These hypothetical strategies proposed various levels of metabolic treatments for HGCM.

A recent article by Seyfried et al. proposed a series of similar strategies called a *Press-Pulse* metabolic cancer treatment [7]. The *Press-Pulse* treatment is based on an evolutionary concept dealing with evolutionary extinctions after gradual environmental changes (*Press*) or after acute disruptive events (*Pulse*) [7,11]. However, both *Press* and *Pulse* left some species alive, either through survival of the fittest in the *Press* or through the physical and biotic environments recovering to their pre-disturbance equilibria in the *Pulse*. It was thus only when both *Press* and *Pulse* occurred simultaneously that mass extinctions without recovery occurred [7,11].

The metabolic *Press* therapy for cancer treatment envisaged by Seyfried et al. *inter alia* entails the long-term management of blood glucose (BG) levels. This is done via a Ketogenic Diet as well as psychological stress reduction [7]. For the short-term metabolic *Pulse* therapy, glucose and glutamine inhibitors are *inter alia* suggested [7]. Other non-metabolic therapies i.e. hyperbaric oxygen, chemo and radiation therapy can also be used as a *Pulse* therapy [7]. The metabolic inhibitors have some problems with toxicity [7].

Abbreviations: BG, Blood Glucose; DCA, Dichloroacetate; ECG, Electrocardiography; EGFR, Estimated Glomerular Filtration Rate; FDG, Fluorodeoxyglucose; GKI, Glucose-Ketone Index; GKIC, Glucose-Ketone Index Calculator; HGCM, Highly Glycolytic Cancers and Metastases; KD-R, Restricted Ketogenic Diet; PET, Positron Emission Tomography; PERCIST, PET Response Criteria In Solid Tumors; SUV, Standardized Uptake Value

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https://doi.org/10.1016/j.mehy.2018.06.014

Received 5 April 2018; Accepted 15 June 2018

In this article the authors propose to add a non-toxic metabolic *Pulse* treatment to the work of Seyfried et al. [7]. The full strategy is also a *Press-Pulse* strategy. In the proposed strategy, the lifestyle intervention (Restricted Ketogenic Diet (KD-R)) [6,7] in combination with stress and blood glucose suppression [6] via *inter alia* atenolol and metformin act as the *Press*.

The hypothesized short-term, severe blood glucose restriction, is new for cancer treatment and is via a combination of pharmacological agents which act as the metabolic *Pulse* therapy. The patient's BG values can be dropped to very low levels, for short periods, in a safe manner. *In vitro* tests showed that BG reduction to 2 mmol/L for 180 min can be an effective cancer treatment [12].

Although BG is usually the main fuel for HGCM cells, glutamine is also an important fuel [4,6,13,14]. The authors have not yet found a similarly non-toxic method of reducing glutamine levels. The current hypothetical treatment methodology focuses solely on glucose deprivation and thus on HGCM treatment. Glutamine deprivation is however a large field to cover and as such deserves a more in-depth analysis. A non-toxic *Pulse* treatment for glutamine will therefore be the focus of a follow-up paper.

Current metabolic control strategies

Short-term (Pulse) pharmacological glucose and glutamine deprivation strategies

The currently recommended glycolysis inhibitor, 2-deoxyglucose (2-DG), has been shown to have therapeutic effects when used in combination with a Restricted Ketogenic Diet (KD-R). However, toxicity has been found with 2-DG [7].

Various compounds are also studied to inhibit the glutamine metabolism cycle by targeting either glutaminase, glutamine transporters or inhibiting glutamine directly [15]. A recent review reported that the three most studied inhibitors namely acivicin, 6-diazo-5-oxo-L-norleucine (DON), and azaserine all revealed degrees of gastrointestinal toxicity and neurotoxicity [16].

The current strategies for the short-term *(Pulse)* deprivation of both glucose and glutamine thus have some problems with the toxicity of the blockers used in the treatment. There is however potentially an alternative way to severely reduce a patient's blood glucose without the concomitant toxicity present in the use of glucose blockers. Such a new *Pulse* method for cancer treatment will be discussed in this paper. Short-term non-toxic glutamine deprivation will be discussed in a future paper.

Long-term (Press) glucose deprivation strategies

In 1921 Wilder developed the Ketogenic diet for the treatment of epilepsy [17]. In recent years the Ketogenic diet has also shown therapeutic effects as a cancer treatment when used in combination with various therapies [18].

These therapies are documented in preclinical studies for several cancers including; breast and ovarian [19,20], colon [21], gastric [22], lung [23,24], neuroblastoma [25,26], pancreatic [23,27] and prostate [28–30] cancers. The preclinical and clinical studies not only improve the treatment effectiveness of conventional therapies, but can safely be applied in cancer patients [23].

The KD-R consists of a standard Ketogenic diet combined with restricted calorie intake. A standard Ketogenic diet in turn consists of a high fat and low carbohydrate and protein diet, where the ratio of fats to carbohydrates and proteins is usually 3:1 or 4:1 [31]. Therefore, by decreasing carbohydrate and calorie intake, the KD-R acts as a long-term glucose deprivation therapy via the reduction of circulating glucose and insulin levels, while elevating ketone bodies [32].

With the reduction of glucose levels, cellular energy is reduced by decreasing glycolytic and pentose phosphate pathways [2,33]. The body makes up for this energy by generating water-soluble ketone bodies (D-β-hydroxybutyrate and acetoacetate) in the liver from adipocyte-derived fatty acids and ketogenic dietary fat. This state is known as nutritional ketosis.

Many types of peripheral cells, including brain cells, do not only use glucose to produce acetyl-CoA for the production of adenosine triphosphate, but can also use ketone bodies. The body is thus forced to burn fat instead of glucose for the generation of energy [33]. Nutritional ketosis can be maintained by the addition of exogenous ketone supplements, such as medium-chain triglycerides, ketone salts and/or esters [34].

Antidiabetic (BG reducing) medicines such as metformin could be used as a long-term *(Press)* BG deprivation strategy [6,7]. Metformin shows a reduced incidence of many different types of cancers, mimics aspects of nutritional deprivation and lowers cancer mortality [35]. Metformin decreases basal glucose by suppressing hepatic gluconeogenesis and glycogenolysis, as well as by increasing glucose uptake in muscle tissue [36]. It also increases free fatty acid utilization, insulin sensitivity and decreases blood insulin levels [36].

Stress is *inter alia* an important contributor to high levels of BG [6,37] as well as elevated levels of glucocorticoids, catecholamines and insulin-like growth factor (IGF-10) all of which promote tumorigenesis [7]. Successful long-term strategies should thus also include the stress management of cancer patients. Multiple stress management techniques such as exercise [6], yoga, music, etc. in addition to pharmacological methods may be used [7].

Methods

Preamble

The proposed metabolic treatment includes both long-term (*Press* [7]) and short-term (*Pulse* [7]) glucose deprivation strategies. Fig. 1 shows the treatment methodology schematically and will be described in more detail in the rest of the article.

All of the suggested procedures are standard, although some procedures are only standard in non-cancer patients. Therefore, in Fig. 1 the procedures are separated into two categories namely standard procedures in cancer patients and standard procedures in non-cancer patients. These two categories are denoted by different coloured check marks in the individual procedures. The important message is that all elements of the suggested treatment have already been proven to be safe for humans.

Cancer identification

Firstly, patients should undergo cancer identification in order to ensure that their cancer is sufficiently glucose avid for the treatment to have an effect. This should be done by using current glucose based positron emission tomography (PET), as shown for Visit 2 in Fig. 1. A non-metabolisable glucose analogue, fluorodeoxyglucose (FDG) is used [38].

A semi-quantitative method, namely standardized uptake value (SUV), should be used to determine the glucose analogue (FDG) uptake [39]. With the evidence of untreated solid tumors typically having a mean SUV value greater than 5.0 [6], it is suggested that only patients with a SUV higher than 5.0 should initially be included in this therapy. This will ensure a high probability that the treatment will show effect.

A modified version of the PET response criteria in solid tumors (PERCIST) evaluation criteria [40], should be used in combination with standard FDG-PET scanning. This will distinguish the metabolic and physical characteristics of the tumor, before and after the glucose-deprivation therapy (Visits 2 and 4 in Fig. 1).

Proposed long-term glucose deprivation (Press)

Long-term glucose deprivation should be done via dietary control and restriction as well as the use of metformin and stress reduction via