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

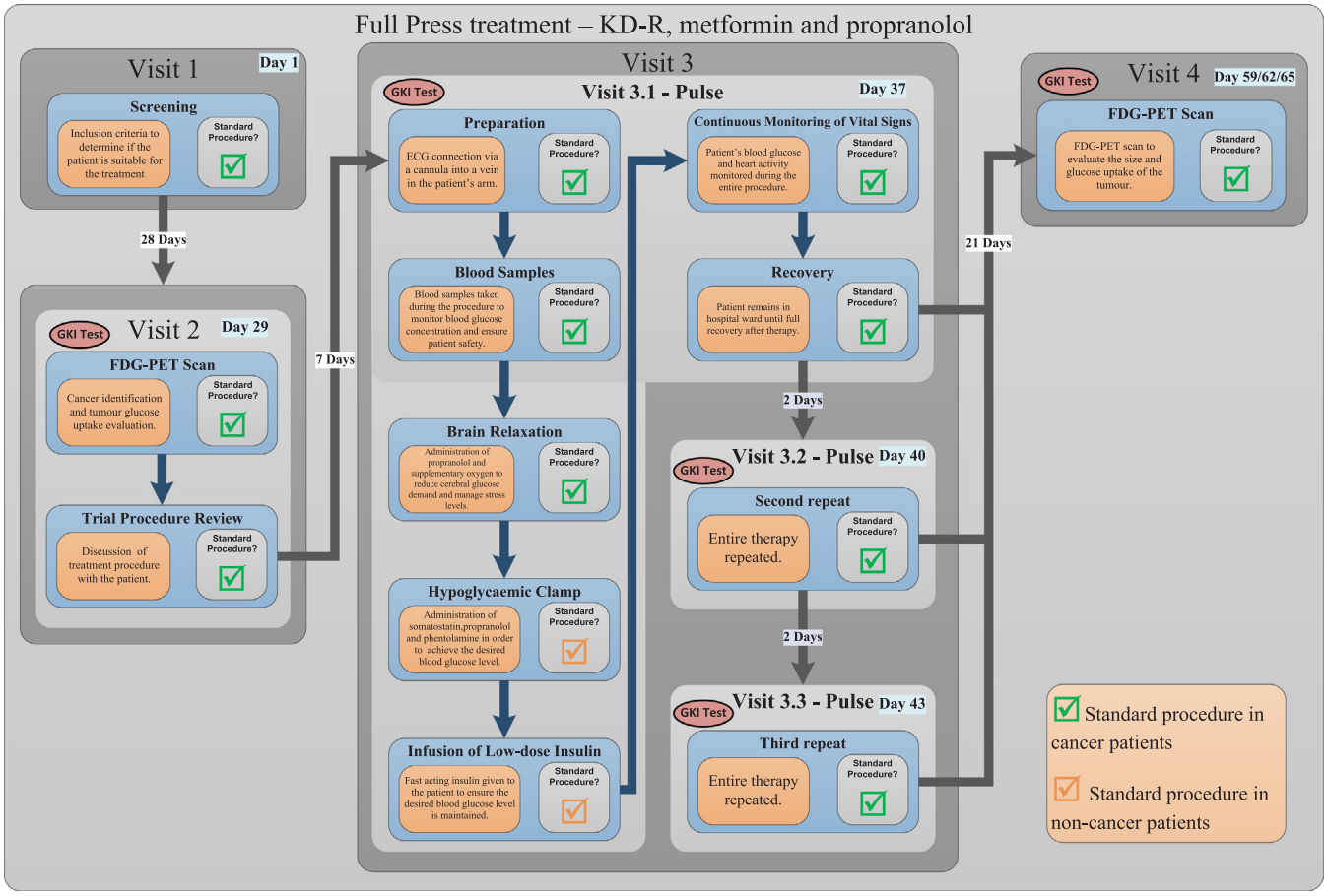

Fig. 1. Proposed *Press-Pulse* cancer treatment. Note: Fluorodeoxyglucose based Positron Emission Tomography (FDG-PET), Electrocardiography (ECG), Glucose Ketone Index (GKI), Restricted Ketogenic Diet (KD-R).

orally administered β-blockers. Metformin will be administered at a single dose of 500 mg per day as per nondiabetic patients. This will be adjusted according to the patients BG level [41].

A recent phase two clinical trial reported on the safety and efficacy of pharmacologically inhibiting β-adrenergic and cyclooxygenase-2 pathways in breast cancer patients via propranolol and etodolac [42]. It was concluded that these inhibitors provided a safe and effective strategy to inhibit multiple cellular and molecular pathways related to metastasis [42].

However, research shows that long-term use of the β-blocker propranolol slightly increases non-diabetic patients' BG levels [43]. Research also shows that propranolol reduces mitochondrial metabolism in healthy tissue [44]. Fortunately, a selective β_1-blocker, namely atenolol, has been shown not to have a significant effect on glucose metabolism [45]. It will therefore be administered to the patients to reduce stress levels. The dosage will be individualized based on the patients' response to an initial daily dosage of 50 mg [46]. The dosages of both metformin and atenolol will be adjusted in the weeks leading up to Visits 3.1–3.3 as seen in Fig. 1.

KD-R can act as a long-term glucose deprivation therapy, whereby circulating glucose and insulin levels reduce while ketone bodies are elevated [27,33,47]. The long-term glucose deprivation should start at Visit 1, in Fig. 1, with the screening visit.

Patients should follow a personalized KD-R throughout the entire treatment. In order to ensure efficacy of the therapeutic effects on HGCM patients, the glucose-ketone index (GKI) of each patient should be monitored via a glucose-ketone index calculator (GKIC) [48]. The patients will undergo a GKI test before each visit, as seen in Fig. 1. A GKI value of less than 2.0 (preferably 1.0) will ensure that the patient is in a manageable ketosis state [48], thus strictly adhering to the KD-R.

Hypothesized short-term glucose deprivation (Pulse)

A combination of *in vitro* studies [12,49] on short-term glucose-deprivation on cancer cells was used to deduce therapeutic periods and the desired blood glucose level required for the present *Pulse* treatment. The current target level of glycaemia is 2 mmol/L [12]. This can be achieved by a combination of low-dose insulin and suppression of the glucose counter-regulation system [50].

Such suppression can be safely done by continuous infusion of somatostatin (to suppress glucagon secretion) and a combination of both α and β-blockers (specifically the adrenergic antagonists, phentolamine and propranolol), to block epinephrine and norepinephrine actions [50,51]. Short-term use of the β-blocker propranolol has been shown to impair glucose recovery from insulin induced hypoglycaemia [52]. This will be beneficial for the short-term *(Pulse)* treatment.

The proposed procedure was successfully carried out in non-cancer patients by Rizza, Cryer and Gerich in 1979 [50]. It was clinically tested on human participants for an *inter alia* 90 min duration at 2 mmol/L blood glucose level.

The proposed short-term glucose deprivation will be a replication of the Rizza, Cryer and Gerich method [50] as the procedure already has ethical approval for non-cancer patients. The only suggested differences will be to firstly double the therapeutic time to 180 min, in order to coincide with our *in vitro* tests [12,49]. The second difference will be the addition of two or three repeating treatments separated by two days (as seen in Visits 3.2 and 3.3 in Fig. 1).

As it is known that cancer patients have unpredictable responses to various treatments, the short-term *(Pulse)* therapy could initially be tested for shorter time frames. Physiological and psychological responses to acute hypoglycaemia could then be assessed.

Although not part of the initial Rizza, Cryer and Gerich method, it should also be investigated to administer exogenous ketone supplements, such as a medium-chain triglycerides l, ketone salts and/or esters to the patients. This should elevate ketone levels to ensure further safety of the brain [33].

Suppression of glucose counter-regulation

In order to achieve blood glucose levels of approximately 2 mmol/L an initial administration of low-dose (0.04 IU/kg) rapid-acting insulin should be administered to the patient [50], illustrated in Fig. 1 as the "Infusion of Low-dose Insulin" step of Visit 3. Such a dose typically achieves blood glucose concentrations of 2 mmol/L within 15 min [50,53]. After the first dose of insulin, the patient should also be given a combination of drugs to suppress blood glucose counter-regulation levels for 180 min, referred to as the "Hypoglycaemic Clamp" step of Visit 3 in Fig. 1.

The suppression of glucose counter-regulation has previously been achieved by the combination of somatostatin, phentolamine and propranolol. The dosages for the respective drugs will be somatostatin at 250 μg/h, phentolamine at 500 μg/min and propranolol at 80 μg/min [50]. However, glucose slowly appears in the plasma during such infusion of these suppressors (which is an inherent safety feature). Therefore, in order to maintain blood glucose levels at 2 mmol/L, supplementary low-dose insulin (0.014 IU/kg) should be administered if necessary.

General effects of pharmacological agents

Glucose counter-regulation agents have various effects on the adrenergic system. The two adrenergic blockers that will be used in this treatment are α and β-blockers. Adrenergic blockers bind to adrenergic receptors, α receptors (located on nerves) or β receptors (located in smooth muscles of the heart, bronchioles, arterioles and visceral organs), but inhibit or block stimulation of the sympathetic nervous system [54].

For the sake of the proposed treatment, α-blockers and β-blockers cause inhibition of both glycogenolysis and gluconeogenesis with α-blockers also inhibiting glucagon release from the pancreas [54,55].

Somatostatin suppresses both glucagon and insulin secretion [56,57]. Although somatostatin is naturally secreted from pancreatic δ-cells (and in the hypothalamus) it is also available in synthetic form as somatostatin analogues [56,57].

Safety of pharmacological agents used in Pulse treatment

Propranolol is a β-blocker, and has been shown to inhibit development of metastases *in vitro* [58] and *in vivo* [59]. β-Clamps also significantly reduce resting energy expenditure in cancer patients [60]. The long-term use of propranolol is further associated with less advanced disease at diagnosis and lower breast cancer-specific mortality [61,62], improved prostate cancer survival and reduced metastases [63].

Up to 30% of women with breast cancer suffer from anxiety and depression, and a history of depression might predict cancer recurrence and overall survival [64]. Perioperative stress and anxiety stimulates the physiological stress response through the hypothalamic–pituitary–adrenocortical axis and the sympathetic nervous system. This leads to secretion of glucocorticoids, endogenous opioids, and catecholamines. These responses lead to immunosuppression, which could promote postoperative metastases [65]. Stress reduction should thus be beneficial for cancer patients, during *Pulse* and *Press* therapies.

A large amount of evidence shows that stress hormones (epinephrine and/or norepinephrine) induce a promoting effect on various tumors, including but not limited to, cancers of breast, colorectal, leukaemia, lung, melanoma, nasopharynx, oesophagus, ovary, pancreas, prostate, hemangioendotheliom and angiosarcoma [66]. Epinephrine and norepinephrine both bind to β_2-adrenoceptors and β_1-receptors respectively [66]. It has thus been proposed that β-adrenoceptor antagonists, such as propranolol and atenolol might inhibit some of the deleterious effects of stress [66,67].

Somatostatin analogues (e.g. octreotide/sandostatin or lanreotide) were found to inhibit growth of pancreatic and breast cancer cells *in vitro* [56]. Somatostatin is also used for treating pituitary tumors, insulinomas and carcinoid tumors [57,68]. Phentolamine has additionally been used for alleviation of pain in some cancer patients [69].

Insulin is a naturally occurring peptide hormone produced by the β-cells of the pancreatic islets. Although there are occasional problems with using insulin, these tend to be problems with dosage administration [70]. The insulin dosages and the patient's BG will thus be continuously monitored to ensure patient safety.

Unfortunately, insulin stimulates glycolysis. Also insulin receptors are overexpressed in cancer cells, which drives cancer growth and proliferation [6,71]. Although the insulin dose in this study is not excessive, similar to basal rates, the authors agree that the use of insulin is not ideal. However, the proposed method has already been ethically approved on non-cancer patients [50] and the authors will therefore not stray from this method for the current study. Future research should focus on alternative methods to reduce BG and simultaneously increase ketone bodies, such as administering ketogenic hypoglycaemic agent 1,3-butanediol [72].

All pharmacological agents used in the proposed procedure are safe for use by humans. It was further shown that most should also have a positive effect on cancer control.

Controlling of cerebral glucose demand

For patient safety it is important to downregulate cerebral glucose demand in a safe manner. This can be done by administering a relaxant [73,74]. In this case the β-blocker propranolol will be used, as discussed in Section "Suppression of glucose counter-regulation". In addition, supplemental oxygen will be administered via a cannula and two prongs in the nostrils, as illustrated in Fig. 1 by the "Brain Relaxation" step of Visit 3. This serves to reduce cerebral glucose metabolism by approximately 20% [75].

Although the proposed glucose deprivation therapy has been carried out previously on healthy patients without permanent adverse neurological effects [50], further caution will be taken with cancer patients. This is discussed in the next section.

Initial extra patient safety precautions

To ensure patient safety, each patient should undergo the short-term (*Pulse)* therapy in a controlled environment of a hospital ward setting. Furthermore, an oncologist and endocrinologist will continuously monitor the patient and oversee the short-term stage of the proposed glucose-deprivation therapy.

A patient undergoing the proposed glucose-deprivation therapy might experience slight hypoglycaemic symptoms. Awareness of hypoglycaemia is mainly the result of the perception of neurogenic symptoms [51], which are largely sympathetic-neural rather than adrenomedullary [76]. Some neurogenic symptoms such as palpitations, tremor, and anxiety are adrenergic whereas others such as sweating, hunger, and paraesthesia are cholinergic [51]. Neuroglycopenic symptoms range from behavioural changes, fatigue, and confusion to seizures and could result in loss of consciousness [51,77].

An important safety measure (as described earlier) is the reduction of the cerebral glucose demands by *inter alia* providing conventional supplementary oxygen. This would minimise possible hypoglycaemic-induced neurogenic symptoms, when blood glucose is reduced to 2 mmol/L. In general, recovery from any acute cognitive decrement after severe hypoglycaemia is complete by 1.5 days [78].

A value of 2 mmol/L was found to be safe by Rizza, Cryer and Gerich [50] without supplemental oxygen. We thus believe that blood glucose levels can safely be lowered to less than 2 mmol/L when supplementary oxygen is administered. This is however a subject for a future paper.

To further ensure safe treatment, emergency glucose infusion would be on hand to correct for excessive hypoglycaemia. Continuous monitoring of the following physiological parameters could also be done initially: blood glucose levels (via blood-gas monitoring), electrocardiography (ECG), blood pressure, heart rate, saturation oxygen, saturation carbon dioxide, arterial pH, Na^+, K^+, Ca^{2+} and Cl^-, as illustrated in Fig. 1 by the "Continuous Monitoring of Vital Signs" step of Visit 3.

In very successful cancer therapy it is possible that rapid cell death of tumorous cancer cells can occur. These dead cancer cells may enter autophagy ("self-eating"), apoptosis ("suicide"), or necrosis ("inflammatory cell death") [79]. It is thus prudent to investigate how the body will eliminate such dead cancer cells.

Acute tumour lysis syndrome results from rapid destruction of malignant cells and is characterized by hyperkalaemia, hyperphosphotaemia, hypercalcaemia, or hyperuricaemia [80,81]. The symptoms of hyperkalaemia, hyperphosphotaemia, hypercalcaemia or hyperuricaemia will continually be monitored during the proposed glucose-deprivation therapy, by taking regular blood samples for blood gas analysis of potassium, calcium, and phosphate.

If symptoms of hyperkalaemia (potassium > 6 mmol/L or 25% increase from baseline), hyperphosphotaemia (phosphorous > 2 mmol/L or 25% increase from baseline), hypercalcaemia (calcium > 1.75 mmol/L or 25% change from baseline), or hyperuricaemia (uric acid > 476 μmol/L or 25% increase from baseline) persist [80,82,83], the patient should be infused with intravenous fluid consisting of isotonic sodium bicarbonate to ensure normal levels of potassium, calcium and phosphate are reached [83,84]. To obtain normal levels of uric acid, rasburicase (or allopurinol) should be administered intravenously at 0.1–0.2 mg/kg over 30 min [80,83,84].

Regarding safety of the long-term *(Press)* therapy, the KD-R has been proven safe [23]. The safety of atenolol, for stress suppression, has been established in the more than 30 years it has been in use [85]. A potential risk factor in using metformin for long-term deprivation is metformin-associated lactic acidosis.

Although this is a potential risk, it is low even in patients with stable, mild to moderate renal impairment. Monitoring of estimated glomerular filtration rate (EGFR) is thus important to ensure metformin-associated lactic acidosis does not occur in patients. A reduction in the metformin dosage is recommended when EGFR is between 30 and 45 mL/min/1.73 m2 and discontinuation of metformin if EGFR is < 30 mL/min/1.73 m^2 [86].

If needed, this could also be mitigated by the administration of dichloroacetate (DCA), which has been used clinically as an investigational drug to treat lactic acidosis [87]. Substantial evidence in preclinical *in vitro* and *in vivo* models show that DCA might have an anticancer effect [88].

Discussion and conclusion

Normal cells have a much lower BG demand than most cancer cells. They are also more metabolically flexible as they can efficiently metabolize nutrients other than glucose (and glutamine). To capitalize on this therapeutic window a BG deprivation treatment method was proposed. (A non-toxic treatment to inhibit glutamine will be discussed in a follow-up paper).

The long-term *(Press)* BG therapy is well-known and was shown to be effective and safe [17,34]. For the hypothesized *Pulse* therapy the following: *In vitro* tests showed that highly glycolytic cancer cells can be severely affected if BG can be reduced to 2 mmol/L for 180 min [12]. It is hypothesized that if this *Pulse* therapy is used *in vivo* and repeated, the cancer cells should potentially receive a mortal blow. The proposed procedure has been safely applied to non-cancer patients [50]. A method to test the hypothetical treatment was also discussed.

The proposed *Pulse* metabolic treatment provides a method to severely reduce blood glucose supply in cancer patients without the toxic effects that posed problems in earlier works [7]. This methodology however only focuses on solving the problem of reducing the blood glucose supply and as such there is a large scope for further refinement of the methodology by combination with other non-metabolic factors.

Cancer cells are shown to be more vulnerable to chemotherapy and radiation, after their metabolic demands have been suppressed [7]; therefore further research of combination therapies is imperative [6,7]. This would identify potential targets for metabolic therapies in combination with chemotherapy, radiation and/or hyperbaric oxygen for the ongoing battle against cancer [6,7].

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data used in this article were sourced from external sources. The relevant sources are referenced in text.

Competing interests

None.

Funding

The research was funded by the first author.

Authors' contributions

All of the authors have been involved in the writing of this manuscript and have read and approved the final text.

Conflicts of interest

None.

Acknowledgements

Prof Leon Liebenberg was involved in the initial research for this article and the work on the glucose cycle was initiated by C. Mathews. The angel investor was Dr Arnold van Dyk.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.mehy.2018.06.014.

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