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Ethische beoordeling	Goedgekeurd
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

Health condition

Glioblastoma Multiforme, ketogenic diet, feasbility, safety, adults, brain cancer, ketosis

Ondersteuning

Primaire sponsor : ErasmusMC

Overige ondersteuning : KWF

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Feasibility of KD during standard treatment with RT and CT defined as successfully following the KD for 14 weeks after start of protocol treatment. So a patient is considered a failure for the primary endpoint if the KD is followed for less than 14 weeks from start of protocol treatment.

Toelichting onderzoek

Achtergrond van het onderzoek

Glioblastoma Multiforme is a malignant brain tumor with grim prognosis. Median survival after standard treatment with surgery, radiotherapy and chemotherapy is only 15 months. Therapeutic drugs have been developed, but they were unable to prolong survival in the past decades. We intend to explore the safety and feasibility of an interesting novel strategy, that is the ketogenic diet (a high fat and low carbohydrate diet) that deregulates the metabolism of cancer cells but not of non-neoplastic cells. High-grade gliomas are known for their high glucose consumption and deprivation of glucose could eventually lead to tumor cell death. Hence, the ketogenic diet could be promising in conjunction with the standard radiotherapy and chemotherapy for the treatment of malignant brain tumors. We will treat 12 adult patients with Gliobastoma Multiforme with Ketogenic Diet for 14 weeks as add on therapy to standard chemo-radiation treatment.

Doel van het onderzoek

Several investigators have suggested using dietary carbohydrate restriction as a therapeutic strategy to allow the host to successfully compete against a tumor [2, 7, 19]. The induced ketosis and increased lipolysis after low carbohydrate diets have been reported to inhibit cancer growth in recent studies in vitro and in vivo [8, 11, 20-22]. Malignant brain tumor cells mainly derive their energy from the anaerobic glycolytic pathway thereby showing an increased glucose utilization in comparison to normal brain. Studies also show that glioma cells are incapable of compensating for glucose restriction whereas normal brain cells can compensate by metabolizing ketone bodies. This suggests a potential disadvantage of tumor cells as compared to normal cells under a carbohydrate-restricted KD [2, 19]. In a mouse brain tumor model of high-grade astrocytoma and glioma, tumor size reduction of 35-65% was observed during treatment by high fat- carbohydrate restricted diets, showing the effectiveness of this therapy [2]. Case reports have shown the effect of KD on tumor growth and survival in two children and one adult patient with progressive glioma treated with KD [9, 19]. Although a 13 year survival in one of these patients suggests a beneficial effect and such a diet appears to be safe and feasible in these patients, no conclusions can be drawn on the effectiveness of KD in these cases.
Although low carbohydrate intake alone has shown effectiveness in the treatment of brain tumors in several animal models and in vitro studies, the combination of a KD with existing therapies may be more effective. Recently, a KD in combination with irradiation in mice with brain tumors showed an impressive synergistic effect of KD as compared to r RT alone [13]. Nine out of 11 mice with brain tumors treated with KD and RT showed an impressive long term survival and eradication of tumor cells. The profound survival increase is not yet clarified but presumed to be caused by increased radiation cytotoxicity of tumor cells as a result of sensitization by this diet [13]. Also, CT toxicities have been reported to decrease in a cancer model in fasting mice and in patients who fasted two to five days before or after CT was started [7, 14, 15]. The protecting effect of fasting or low glucose levels have also been shown in several neurodegenerative diseases in humans [16, 17]. Although the exact mechanism is unknown, cells harboring low glucose levels appear to be better protected

against oxidative stress.
Any adverse effects of carbohydrate-restricted diets have not been reported in healthy subjects, diabetics, or in individuals seeking weight loss over a long term period [23-26]. Recently, a group of investigators in New York has shown the safety and feasibility of carbohydrate restriction in 10 adult patients with advanced (non-brain) cancer [10]. The study showed that a low carbohydrate diet is safe and feasible in selected patients with advanced cancer. The extent of ketosis, correlated with stable disease or partial remission [10]. A recent retrospective study of six GBM patients who were on an uncontrolled KD on their own initiative concluded that the KD was safe and well tolerated during standard treatment of GBM [18].
In summary, a KD has two potential beneficial effects in cancer treatment: sensitizing tumor cells for toxic effects of RT and protecting normal tissues from toxic side effects of CT. Following these findings, we are exploring the use of the KD as a treatment option for brain tumors during standard treatment. Safety and feasibility need to be known before efficacy can be studied.

Onderzoeksopzet

The standard treatment of GBM patients consists of tumor resection followed by combined RT and chemotherapy (CT) for a period of six weeks after surgery and subsequent monthly cycles of chemotherapy mostly during six months. During standard treatment the patient will receive KD during the study period of 14 weeks. The patient follows a strict diet with high fat and low carbohydrate content which induces ketosis. The patient will be closely monitored by a specialized dietitian and nurse practitioner. The patient related possible risks of the combination of standard treatment and KD are classified as low based on a previous explorative study performed elsewhere[18]. During the 14 weeks study period, safety and feasibility will be assessed by registering the adverse effects of standard treatment and KD, protocol compliance and neurological functioning.

Onderzoeksproduct en/of interventie

Addition of a KD to the Standard therapy consisting of combined temozolomide and radiotherapy in patients after (partial resection of Glioblastoma Multiforme,

Contactpersonen

Publiek

A
Vincent

Wetenschappelijk

A
Vincent

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Inclusion criteria part A
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Histologically proven GBM (Astrocytoma WHO grade 4) after surgical resection
- Age ¡Ý 18 years.
- Amenable and planned for standard RT and CT and starting within 6 weeks after enrolment.
- Supportive partner or family member who can and is willing to help calculating, preparing and providing the meals.
- KPS ¡Ý70.
- Written informed consent
- Able and willing to complete study specific diaries and questionnaires.
- Able to understand the procedures and instructions and able to give informed consent
Inclusion Criteria part B
Able to reach 3+ mmol/L ketosis within one week on the KD
- Abe to follow the KD after reaching ketosis, for at least 3 days

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Neurological deficit in language or cognitive functions causing inability to fully understand the study protocol and requirements
- Dementia or amnesia
- History of psychiatric disorder that would prohibit the understanding and giving of informed consent
- The use of dexamethasone at time of registration
- Fatty acid disorders (like Medium Chain triglycerides disorders)
- Hypertriglyceridemia (> 10 mmol/L) despite treatment
Hypercholesterolemia (> 7.5 mmol/L) despite treatment
- Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) >2.5x ULN

- (History of) Kidney stones
- Diabetes mellitus
- (History of) Pancreatitis
- Acute/chronic gastro-intestinal disease(s) such as persistent diarrhea, colitis ulcerosa and M. Crohn
- Underweight (BMI < 16)
- Overweight (BMI >30)
- Carbohydrate content of any concomitant medication exceeding 1000mg with no suitable alternatives
- Untreated or uncontrolled hypertension
- Any other chronic or systemic disease or serious medical condition (other than related to GBM), that may influence protocol compliance or outcomes of the study significantly

Onderzoeksopzet

Opzet

Type :	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel :	Anders
Toewijzing :	Geen controle groep
Blindering :	Open / niet geblindeerd
Controle :	N.v.t. / onbekend

Deelname

Nederland

Status :	Werving gestopt
(Verwachte) startdatum :	01-02-2015
Aantal proefpersonen :	12
Type :	Werkelijke startdatum

Ethische beoordeling

Goedgekeurd

Datum :	29-01-2015
Soort :	Eerste indiening

Registraties

In dit register bekende (historische) registraties

Geen registraties gevonden

In overige registers

Source : NTR

Register	ID
NTR-new	NL5021
NTR-old	NTR5167
CCMO	NL5062507814

Resultaten