ERGO2: A prospective randomized trial of a 9-day schedule of calorically restricted ketogenic diet and fasting or standard diet in addition to re-irradiation for malignant glioma

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Study protocol by PD Dr. J. Rieger, Prof. Dr. C. Rödel, Prof. Dr. J. Bojunga, PD Dr. E. Hattingen and Prof. Dr. J. Steinbach

Study endpoints

The aim of the study is to investigate the efficacy, safety and feasibility of a caloric restriction in combination to a re-irradiation in patients with recurrent glioblastoma.

Primary endpoint

- Rate of progression free survival at 6 months

Secondary endpoints

- Safety and feasibility of the diet
- Rate of progression free survival at 6 weeks, 3 and 12 months after start of intervention
- Duration of local control (local progression free survival)
- Local control at 6 weeks, 3 and 12 months
- Overall survival after start of intervention
- Frequency of epileptic seizures
- Rate of ketosis evaluated by blood samples
- Quality of life
- General mood / depression (SCL-90R-Analysis)
- Cognitive function (d2-Test)
- Metabolism in MR-Spectroscopy

Selection of patients

Fifty patients with recurrent glioblastoma after treatment with radiation and temozolomide and indication for re-irradiation according to tumor board recommendation will be included in the trial.

Eligibility criteria

- Age of 18 years or older
- Histologically confirmed glioblastoma or gliosarkoma
  or malignant progression of a lesser grade tumor in MRI
- Inclusion after at least six month from first tumor resection
- Prior radiation therapy of the tumor at least 6 months before inclusion
- Prior therapy with temozolomide
- Multidisciplinary tumor board recommendation for re-irradiation

- Karnofsky performance score (KPS) ≥60% (ECOG ≤ 2)
- Estimated life expectancy of more than 12 weeks
- Serum creatinine < 1,5 mg/dl, urea < 50 mg/dl
- International Normalized Ratio (INR) ≤ 1,5 Glutamat-Oxalacetat-Transaminase (GOT) ≤ 7 x upper limit of normal, Glutamat-Pyruvat-Transaminase (GPT) ≤ 7 x upper limit of normal

Ineligibility criteria

- Bowel obstruction
- Insulin-dependent diabetes
- Decompensated heart failure (NYHA > 2)
- Myocardial infarction within the last 6 months
- Prior atrial fibrillation or ventricular arrhythmia
- Severe acute infection
- Malnutrition / cachexia (Body Mass Index < 18)
- Any serious or uncontrolled medical disorder besides the glioblastoma that, in the opinion of the investigator, may increase the risk associated with study participation or impair the ability of the subject to receive protocol therapy
- Pregnancy or breast-feeding
- Known non-euthyroid thyroid disease
- Known symptomatic decreased pancreatic function
- Dementia or other medical conditions which could impair the ability to adhere to the diet
- Subjects unable (eg, due to pacemaker or ICD device) or unwilling to have a contrast-enhanced MRI of the head

Reasons for early cessation of trial therapy

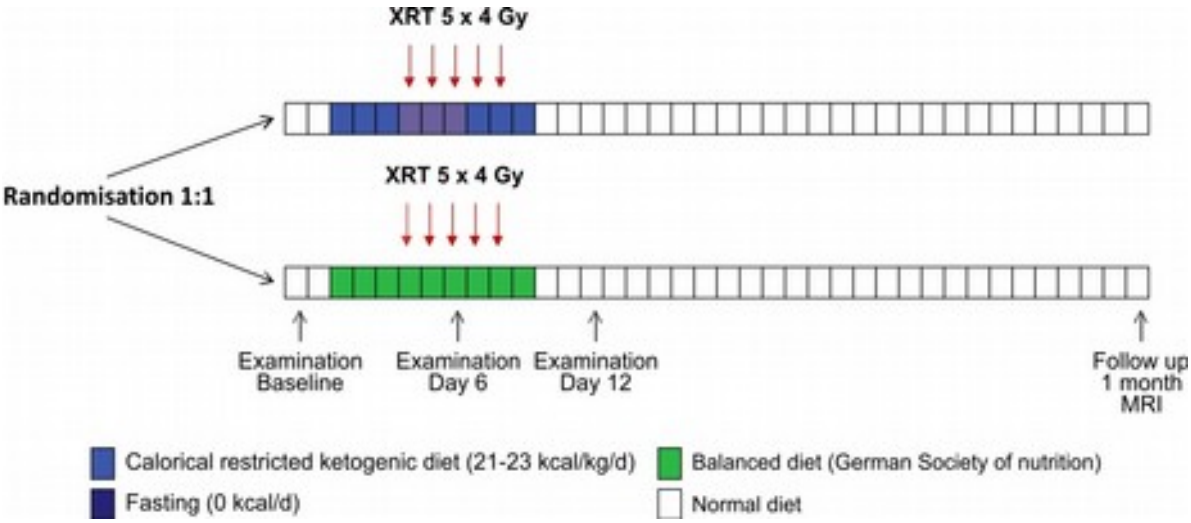
- Patients wish / retraction of consent
- Weight loss of more than 10% of the initial body weight during intervention
- Severe symptomatic hypoglycemia
- Marked clinical deterioration
- Any non-hematological WHO grade 4 toxicity related to the diet

Treatment plan

The treatment schedule is summarized in Figure 1. Radiation therapy was proposed to consist of 5x4 Gy from day 4 - 8 in both groups but other regimens such as 10x3.5 Gy were allowed as well. Patients in both arms received counseling from a professional dietician. In the experimental KD-IF group, patients underwent a dietary intervention over nine days that consisted of two calorically-restricted KD 3-day intervals flanking 3 days of fasting. Calorie restriction was defined as 21-23 kcal per kg body weight, which corresponds to 73% of the estimated calorie requirement for adults with low activity. Carbohydrates were limited to 50 g/d. The patients fasted on days 4-6 with unlimited intake of fluid. From day 10 onwards, patients had no dietary restrictions. For patients in the standard diet (SD) group, nutrition counsel was given adhering to the recommendations of the German Society of Nutrition for cancer patients without advice of calorie restriction. Accordingly, a calorie intake of approximately 30 kcal/kg was recommended (approximately 60-80 g fat, 5 g/kg carbohydrates and 0.8 g/kg protein).

Diet was terminated in the following case(s): weight loss of more than 10% of the initial body weight, severe and symptomatic hypoglycemia or any WHO grade 4 toxicity possibly related to the diet.

Figure 1: Schematic overview of the ERGO2 Trial



The patients were randomized 1:1. The ketogenic group (KD-IF) started with a caloric restricted (21-23 kcal/kg) ketogenic diet on days 1-3. Patients fasted on days 4-6. Days 7-9 were again a caloric restricted (21-23 kcal/kg) ketogenic diet. From day 10 the patients had no dietary restrictions. Patients of the control group (SD) were counseled according to the recommendations of the German Society of Nutrition, no caloric restrictions were advised. Radiation therapy (XRT) was advised from day 4 - 8 but final specification was left to the

local radiation therapist. Clinical examinations were scheduled on day -1 (baseline), day 6 and day 12. First MRI was performed after one month.

Measurement of treatment effect including response criteria

At baseline (day-1), day 6 and day 12 patients were followed by neurological examination, measurement of body weight, Karnofsky Performance Score (KPS), Mini-Mental-Status-Test, d2 test of attention, SCL-90®-Test and EORTC Quality of Life Questionnaire. Additionally, a short questionnaire of 8 aspects concerning the tolerability of the diet was handed out. Further, patients were asked to fill out a dietary diary for days 1 to 12. At baseline, day 6 and day 12, blood samples were collected. Ketone bodies were measured with the Precision Xceed (Abbott Diabetes Care Ltd.). Other parameters included a differential blood cell count, electrolytes, glucose, HbA1c, transaminases, bilirubin, C reactive protein, creatinine, urea, uric acid, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, lipase, total protein, albumin, insulin, Insulin-like growth factor 1 (IGF-1) and ketone bodies.

Magnetic resonance imaging (MRI) was performed at 1.5 or 3 tesla scanners acquiring at least T1-weighted sequences pre- and post i.v. application of gadolinium-based contrast agent and T2/FLAIR-weighted sequences. The first MRI follow-up was scheduled one month after completion of re-irradiation. Further MRI controls were performed in intervals of 2 to 3 months. MRI was analyzed by an experienced, board-certified, neuroradiologist based on response assessment in neuro-oncology (RANO) criteria blinded for dietary allocation of the patients.

Statistical section

In the APG101 trial, the primary endpoint showed a poor outcome with a rate of progression free survival (PFS) at 6 months (PFS6) of only 3.8% in the re-irradiation only arm. We estimated that the additional caloric restriction could raise the PFS6 to 30%. With alpha at 0.05 sample size calculation resulted in 23 patients for each group. Taking a possible dropout rate of 10% into consideration we plan to include 25 patients for each group.

Microsoft Excel (Office 365) will be used for data collection and overview, SPSS Statistics for survival analysis.