Reviewer’s report

Title: Ketogenic Diets as an Adjuvant Therapy in Glioblastoma (The KEATING Trial): Study Protocol for a Randomised Pilot Study

Version: 1 Date: 05 Jul 2017

Reviewer: Thomas Seyfried

Reviewer's report:

Comments to the authors

The authors have not adequately addressed most of this reviewer's previous concerns and recommendations. The study, as designed, will add little new information to what is already known about KD feasibility or deliverability in patients with brain cancer. Moreover, the authors seem unfamiliar with the underlying metabolic problem in malignant brain cancer. Although the study could be a waste of time and resources, I agree that the study should be conducted. It is possible that a few positive patient responses might change the author's largely negative view of the KD as a viable therapy for brain cancer.

1. The authors have used an arrogant tone in their responses to some of the issues raised with their trial. This tone might be fine if they had extensive experience in the subject area. It is clear from their peer-reviewed publications that the authors have minimal experience in the biochemistry of brain cancer or in using ketogenic diets for cancer management. The authors mention that they are not testing efficacy at this stage, but rather the feasibility and deliverability of the diets. A number of feasibility and deliverability studies of KD therapy have already been published for various cancers including brain cancer. Most cancer patients tolerate the diet well. This is discussed at length in the Klement paper, which is now peer-reviewed (Med Oncol 34:132, 2017, DOI 10.1007/s12032-017-0991-5). The author's subjective opinion in stating that, "Klement provides his own opinion of the literature, with a poorly conducted literature review, published in a non-peer reviewed source", speaks to the author's general unfamiliarity with this field. This view is supported further from their comments on the value of the Winter et al review published in Critical Reviews in Oncology/Hematology. R. Klement and the Winter et al group have a distinguished record in the field and are familiar with key issues.

2. The absence of a stand-alone KD group remains as the most serious flaw in the protocol design. Their response to "reviewer 2, point 1, amended with rationale", is inadequate. A healthy eating diet' would "not" be a good control arm, as the authors suggest. This is often referred to as "best supportive care", which is poorly defined (Zafar et al., J. Clin. Oncology,
The appropriate control group would be a KD, either MCT or MKD, used without radiotherapy, TMZ, or steroids. This group would more closely parallel the experimental design in noted animal studies. The authors need to explain why they cannot include this important control group at this time. They attempt to address this issue in their response stating, "A stand-alone group, who are not provided with the current, evidence based, standard of care would raise strong ethical concerns". This might be the case for a "best supportive care" group, but perhaps not for an MCT alone control group. Papers have been written showing how current toxic standards of care contribute to the recurrence of tumor growth. It is the current standard of care for GBM that should raise strong ethical concerns. How might those in the GBM field respond if the author's trial demonstrates that feasibility, deliverability, and therapeutic efficacy of a stand-alone KD is better than that seen in the other groups?

3. Another flaw is the author's preconceived notion that, "personal experience of patients using ketogenic diet so far is that all patients succumb to tumour recurrence and death." This notion speaks further the author's unfamiliarity and denial of observations in the brain cancer field that have been either published or unpublished.

4. The author's mention at the end of comment #5 that, "Ketone testing is an additional research cost for a diet which may or may not provide any patient benefit". The authors are likely correct regarding this point, as the current design of this trial is not likely to provide much new information or much benefit to the participating patients. Their argument about the cost of pee strips vs. blood monitoring would be laughable if people's lives were not involved. The authors go on to mention that, "Recent evidence has also found the ketones may not be the cause of the positive response seen in animal models, but fatty acids (Martuscello et al., 2015), therefore ketone testing may be less important than first thought." There is no information in the Martuscello et al paper to support this statement. These opinions make no sense in light of the metabolic disturbances documented in neural tumors and highlight further the author's unfamiliarity with the biochemistry of GBM and cancer in general.

5. Unfortunately, the authors possess neither the biological knowledge nor prior experience in the field to adequately conduct this trial or to interpret the data. The author's comments and viewpoints suggest that they are entering this trial with a preconceived notion that feasibility and deliverability of the KDs will be difficult and will not show therapeutic benefit.

6. Two bright spots in the protocol are: (1) they will implement a somewhat rigorous KD concurrent with the SOC for newly dx GBM rather than waiting for recurrence, and (2) despite all the limitations, they might see an improvement in progression-free and/or overall survival in one or both of the KD groups when compared to standard of care. In the author's world, a benefit of just 2 months might be considered "significant". Most GBM patients treated with a rigorous KD, where reduced blood glucose is coupled with therapeutic ketosis, beat those stats better than what the authors note in their abstract.
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