Author's response to reviews

Title: Early termination of ISRCTN45828668, a phase 1/2 prospective, randomized study of Sulfasalazine for the treatment of progressing malignant gliomas in adults

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Author's response to reviews: see over
Dear Editor,

Please find attached the revised version of our manuscript # 1676373258270843 that we would like to submit for publication in BMC cancer.

We wish to thank the reviewers for their comments regarding their interest in our work, and are grateful for their comments and suggestions, which we address in the present version of the manuscript. The conclusions of the manuscript/abstract have also been softened in order to take these comments into consideration.

Specifically,

1. Reviewer #1 did not ask for revisions;
2. Reviewer #2 proposed several modifications, which have been dealt with as follows:
   - Major points:
     A. We evidently acknowledge that the small sample of the reported series does not allow for conclusions regarding the efficacy or lack of efficacy of Sulfasalzine for the treatment of recurrent gliomas. The study was indeed designed to accrue 20 patients, but was ended prematurely following the planned interim analysis and given the high incidence of adverse effects and lack of obvious tumor response in the first 10 patients. We also recognize that our patients presented with large tumor burdens and that this may also have prevented the observation of clinical responses. In order to further clarify these points, the conclusion of the abstract was altered as follows:

   **Conclusion:** Although the proper influence of sulfasalazine treatment on patient outcome was difficult to ascertain in these debilitated patients with a large tumor burden (median KPS=50), ISRCTN45828668 was terminated after its interim analysis. This study urges to exert cautiousness in future trials of Sulfasalazine for the treatment of malignant gliomas.

   the fifth paragraph of the discussion was also amended:

   Tumor growth was at best unaffected in our patients following sulfasalazine treatment, in contrast to previous reports of tumor growth inhibition in preclinical in vivo models of human malignant gliomas [2, 15]. Several factors might contribute to this discrepancy. First, the small number and large tumor burden of the patients analyzed in this study may have missed or masked a limited drug efficacy. Second,…

   B. We agree with the fact that tumor growth may have been responsible for some of the side effects encountered in this study, and this is stated in the results section (“Even though the initial KPS of these patients were 40 and 50 respectively at the time of inclusion, these adverse events were considered as probably related to the study drug”). However, it is the very principle of any phase I study to mention all adverse events encountered under treatment protocol. Further, although sulfasalazine has been used for decades in the treatment of inflammatory bowel diseases, non data is available in the population of patients with brain tumors and there is an increasing number of case reports that show that this drug may very well have central nervous system side effects in patients with or without pre-existing neurological disease. One can thus not dismiss these side effects as the pure result of tumor progression on assumptions of clinical safety of the drug. In fact, it was one of the very purpose of the study to assess the potential toxicity of sulfasalazine in debilitated brain tumor patients. To moderate our conclusions however, we have changed the manuscript as follows:
Discussion, third paragraph:

*Whatever the exact mechanism, and although tumor progression may also have contributed to this effect, sulfasalazine treatment induced a significant brain edema in 50% of our recurrent glioma patients, which likely contributed to worsening of their headaches and neurological condition.*

Discussion:

*The death of two patients during or shortly after sulfasalazine treatment raises significant concerns about the safety of this drug for the treatment of human malignant gliomas, even if continued tumor progression in these already debilitated patients (KPS of 40 and 50, respectively) may have contributed to their deaths. In agreement with the independent review committee of the study, these serious adverse events and apparent lack of therapeutic benefit led to the early termination of ISRCTN445828668.*

- Minor points:
  1.) Table 2 has been modified in order to provide Grade 3 AE as well;
  2.) Tables 1 & 2B have been altered and grouped as tables 1 A&B
  3.) The paragraph over these statistics has been deleted, and the Material and methods section has been altered accordingly
  4.) and 5.) The paragraph has been modified as requested, and data are also provided in table 1B;

We do believe that all comments and suggestions of the reviewers have been taken into account correctly, and we hope that our modifications to the manuscript will render it suitable for publication. We remain yours for any additional information you might require.

Sincerely,
Pierre A Robe, MD, PhD