Reviewer's report

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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Reviewer: Christoph Beier

Reviewer's report:

Robe et al. describe the results of an interim analysis of a phase I/II trial investigating Sulfasalazine for the treatment of progressive malignant gliomas. Based on the analysis of 10 patients randomized into 4 different dosing groups the authors conclude that Sulfasalazine is neither safe nor effective. Unfortunately, the study does hardly allow any conclusions on the efficacy and the safety of Sulfasalazine.

Major points:

1.) The authors claim that Sulfasalazine lacks apparent efficacy. This conclusion is not possible based on the data presented. The treatment of 10 high risk patients (median KPS 50% (!), median tumor volume 67ml, pretreated recurrent tumors) in 4 different dosing groups does not allow any conclusions on the efficacy of a given treatment. A direct comparison with previous studies is not possible because of the bad clinical status of the patients. Still, a comparision may be informative: In the study of Yung et al. (British Journal of Cancer, 2000) only 51 of 112 patients receiving temozolomide and only 37 of 113 patients treated with procarbacin showed an objective response (i.e. stable disease or partial response). Having these numbers in mind, it is not possible to conclude that sulfasalzine is not effective. In these high risk patients, one can not expect high response rates even if the drug may be effective per se.

2.) The authors claim that sulfasalazine causes a high incidence of serious adverse events. Again, this conclusion may be correct but can not be concluded based on the data described. The two deaths occurred in the lowest (!) dosing a group and may not be treatment related but resulted simply from tumor progression. In addition, almost all grade 4 toxicities were neurological deficits which are always difficult to evaluate. Knowing that sulfasalazine is used for decades for inflammatory bowel diseases in concentrations up to 6 mg and is well tolerated in these patients (the vast majority of these patients without cerebral edema), one can not conclude that this drug must not be used for brain tumor patients.

Minor points:

1.) Please also give grade 3 toxicity in table 2A
2.) Please fuse table 1 and table 2B to allow a quick overview over all patients.

3.) 1st page of the Results part, last paragraph. Statistic on 4 groups with a total of 10 patients is not helpful. Please delete this paragraph

4.) 3rd page of the Results part, paragraph “Secondary objectives: progression free survival…” Please just describe the data (OS, PFS) but avoid any statistical analysis.

5.) Again, the patient number is much too low for this kind of analysis.

Taken together, the data presented do not allow any final conclusions. It “only” warns and urges to exert extreme care in the surveillance in ongoing trials using this or similar drugs.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.