Reviewer’s report

Title: The prospective application of a hypoxic radiosensitizer, doranidazole (PR-350) to rat intracranial glioblastoma with blood brain barrier disruption

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Reviewer: Gelareh Zadeh

Reviewer’s report:

1. Overall the manuscript would benefit from significant editing with regards to language, grammar and spelling mistakes.

Some sentence structures are unclear and as a result the message is lost in their manuscript. For example the opening sentence of the abstract is poorly written. The last sentence, first page of introduction refers to glioma subtypes of various status - what does this mean.

They initially discuss the Blood Brain Barrier (BBB) as a concern for drugs to reach the brain however towards the end of the introduction they also comment that in the case of intracranial tumors there is no BBB. They need to be more detailed and precise about what the issues concerning BBB are.

2. The idea and rational for the project is sound.

3. The experimental approach is good however the authors do not present all the pertinent data related to the experimental design they outline.

4. The methods are explained reasonably well. The pivotal information missing is what level of hypoxia (percentage hypoxia) they treated the cells - invitro and how they performed the clonogenic assay following hypoxia treatment?

5. MRI studies have been detailed sufficiently. However whether interpretation of contrast enhancement can be attributed directly to BBB disruption is not established or an accepted conclusion.

6. Results:

6a. Degree of hypoxia treatment is not stated. Was there different levels of hypoxia treatment? A dose or degree of hypoxia curve for which the compound can be effective will be useful to provide and establish.

6b. Evan’s blue images are not convincing for disruption of the BBB. Clearer images - perhaps with the brain removed from the background tissue and cross sections (coronal) will help demonstrate extent and regions of Evan’s blue extravasation.

Since there is known Evan’s Blue extravasation into intracranial xenografts the need for mannitol disruption of BBB is not entirely clear to me. This also relates to the point above i make as to whether the authors believe BBB is intact in the tumor or disrupted. If disrupted why is there a need for Mannitol?
6c. Pimonidazol has been used in the animals. Figure 4C demonstrates this within the tumor. There is no attempt or data shown to demonstrate how the levels of hypoxia then vary with treatment. The IHC for Pimo. is clear but not sure what the authors are demonstrating with this?

6d. There is no histological analysis of the treated tumors. The only end point is tumor volume. Further characterization of the tumors on histology or MRI parameters, level of enhancement or contrast uptake, for example will be useful data to provide.

Overall, I think the manuscript will require significant revisions including additional experiments to be reconsidered for publication.

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no conflict of interest or any declaration of competing interests to report.