Reviewer's report

Title: Boron neutron capture therapy induces apoptosis of glioma cells

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Reviewer: Amanda E Schwint

Reviewer's report:

This study contributes to the knowledge of BNCT radiobiology, essential to the optimization of the therapeutic efficacy of BNCT. It involves extensive exploration of some of the mechanisms underlying the effect of BNCT on glioma cells in vitro. The data are contributory and worthy of publication. However, the following issues should be addressed:

1. Title: the authors study different aspects of the effect of BNCT on glioma cells. Perhaps the title should not be restricted to the apoptosis end-point.
2. Abstract: Line 1: BNCT is not really a “novel” radiotherapeutic strategy—perhaps non-standard is a better term...
3. Abstract: “showing high efficiency for treatment of glioma”- the data available to date do not evidence “high efficiency”.
4. Tumors can always be destroyed. The limitation is the potential damage to normal tissue associated to therapeutic efficacy in tumor tissue. The authors do not discuss this issue anywhere in their manuscript. No reference is made to boron content in normal brain tissues (the boron content in normal brain would limit the exposure time in a clinical context), or potential dose-limiting damage in normal brain tissue. This issue should at least be discussed. What would be the cost in terms of normal tissue toxicity of the potentially therapeutic doses evaluated?
5. The authors should discuss the constraints involved in extrapolating in vitro data to an in vivo context.
6. The authors should comment on the differences between the cell lines employed and the differences in response between the cell lines.
7. Please comment on the choice of BPA dose employed.
8. Was the BPA-containing medium removed prior to irradiation?
9. Because the authors did not include a “BPA only” group they should at least comment on potential effects of the compound alone (no neutron irradiation).
10. It would be useful to see a table with the dose components of BNCT.
11. It would be useful to see the irradiation exposure times in each case.
12. Hoechst staining: the authors refer to cells treated with BNCT. Weren’t the other groups stained as well?
13. In all cases the authors should say if the data are the result of single,
duplicate, triplicate experiments...

14. Fig. 1: the highest value seems to correspond to the U251 cell line. However, in the text the highest value corresponds to the U87 cell line.

15. The authors should quote the doses corresponding to irradiation with neutrons alone (same exposure times as the BNCT groups).

16. What time point do the apoptosis rates correspond to?

17. Discussion: paragraph 3: previous studies by different authors have described BNCT-induced apoptosis – thus it is not correct to state that “the pro-apoptotic effect of BNCT can be proved by our research for the first time”.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests