Reviewer's report

Title: Pentoxifylline sensitizes human cervical tumor cells to cisplatin-induced apoptosis by suppressing NF-kappa B and decreased cell senescence

Version: 1 Date: 22 June 2011

Reviewer: Marzia Pennati

Reviewer's report:

The manuscript describes the effects of Pentoxifylline in combination with cisplatin in cervical carcinoma cell lines (HeLa and SiHa), as well as in immortalized keratinocytes (HaCaT cells). The basic finding is that exposure to Pentoxifylline significantly decreased tumor cell growth and sensitized tumor cells to cisplatin. By contrast, Pentoxifylline alone or in combination with cisplatin minimally affected the growth of normal cells.

In my view, the paper adds little to the literature and do not provide significant evidence concerning the effects of Pentoxifylline in combination with cisplatin in cervical carcinoma cells. Although the idea of the research is interesting, the paper does not warrant publication in its present form. My recommendation would be to better explore the mechanism responsible for the effects mentioned above before re-submitting the manuscript for consideration.

Specific comments:

1. The authors state that in vitro exposure of cervical carcinoma cells to Pentoxifylline enhances cisplatin-induced apoptosis levels. The authors' results are not convincing. In fact, while the combined treatment effectively reduced cell survival in both cell lines (see Figure 1), the same treatment schedule did not result in an increased apoptotic response (as shown in Table 2 and Figure 2 A-B): the percentage of Annexin-positive cells after combined treatment is lower than that observed after exposure to Pentoxifylline alone. The authors should clarify this point.

2. How was defined the treatment schedule to be used for the drug combination? Authors should clarify this point.

3. The method described by Chou and Talalay should be used to determine the nature of the interaction between Pentoxifylline and cisplatin.

4. The formula to calculate the surviving fraction (which is reported in the “Methods” section) is not correct. The surviving fraction should be calculated as follows: surviving fraction = (plating efficiency of treated sample) / (plating efficiency of control).

5. The authors should analyze the effects of the treatments on caspase-8 activity.

6. The authors demonstrated by Real Time PCR that combined treatment modified the gene expression of factors involved in the regulation of apoptosis (i.e., caspase, pro-apoptotic and anti-apoptotic factors). The authors should also
verify the cellular localization of the protein involved in the regulation of the apoptotic machinery after treatment.

Minor points:
- Verify the Figure legends.
- Page 13, line 21: Remove “treatment”.
- Page 38, line 7: Remove “Table 2”.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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