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OPEN PEER REVIEW

Cytotoxicity of Taxol in Combination with Vincristine and Vinblastine Against A375 Cell Line

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 9 Apr 2021 – 17 Apr 2021

Referee 1 Reviewer

MAJOR REVISION 9 Apr 2021

The authors studied the cytotoxicity of Taxol in combination with Vincristine and Vinblastine against the A375 cell line. The idea is novel. Still, the authors need to address some issues or correct some parts of the manuscript. The manuscript is poorly written and warrants extensive grammatical improvement before proceeding.

- In the Abstract, replace " on the human malignant melanoma A375 cells as well as on the non-cancerous human fibroblast HU2 cells" with "against human malignant melanoma A375 cells and non-cancerous fibroblast HU2 cells "
- In the Abstract, the authors claimed that they combined four agents to seek possible side effects of the drugs. How is that possible?
- In the Introduction, the first sentence is too lengthy! Try to use shorter sentences throughout the manuscript.
- In Methods, the authors should mention the concentration of penicillin and streptomycin contained in the DMEM culture medium.
- Why did the authors choose these cell lines? Kindly explain in the Introduction.
- In all treatment groups, the studied anti-cancer agents have shown greater cell-killing effects on A375 cells than on normal human cells. How do you explain these findings? Kindly discuss them.
- On what basis did the authors choose the range of escalating concentrations (7.5 to 240µg/mL)?
- The authors should provide the limitations of their study at the end of the discussion.
- The combination of two or more agents must be performed based on the Chou-Talalay method. Randomly combining agents will not indicate the interaction between drugs and therefore yields no reliable conclusion. The Chou-Talalay method for drug combination is based on the median-effect equation, derived from the mass-action law principle, which is the unified theory that provides the common link between single entity and multiple entities, and first-order and higher-order dynamics. In this equation, the combination index (CI) defines Synergism (CI<1), Additive Effect (CI=1), and Antagonism (CI>1). In this respect, the authors need to clarify why they did not use the Chou-Talalay method and consider it as a limitation to their study.

Associate Editor

MAJOR REVISION 16 Apr 2021

Dear editor
The manuscript needs major revision according to the comments of reviewers.
Best regards

Editor-in-Chief

MAJOR REVISION 17 Apr 2021

Based on the reviewers' comments and my reading of the manuscript, major revisions and a point-by-point response to the comments are needed.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

We would like to thank the reviewers for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Correction has been made in the revised manuscript as follows.

Reviewer 1:
1- in line 29, gene therapy is a better expression.

Correction has been made in the revised manuscript.

2- it is better that the Experimental design section put before the MTT assay section.

Correction has been made in the revised manuscript.

3- in the introduction, explain more about the reason for this combination of strategies. What is the reason for choosing these drugs for combination therapy?

Correction has been made in the revised manuscript.

4- Explain the reason for choosing the combined doses.

Combination therapy is a promising strategy for reducing the side effects of drugs, which are combined with other chemotherapy treatments to enhance their effects.

5- please revise the figure's caption. for example, it's better to divide the figure's caption into a, b and etc subsection.

Correction has been made in the revised manuscript.

6- Please, more discuss about the effect of drugs on HU2 cells in the discussion section.
Correction has been made in the revised manuscript.

Reviewer 2:
The authors studied the Cytotoxicity of Taxol in combination with Vincristine and Vinblastine against A375 cell line. The idea is novel. Still, the authors need to address some issues or correct some parts of the manuscript. The manuscript is poorly written and warrants extensive grammatical improvement before proceeding.

- In Abstract, Replace " on the human malignant melanoma A375 cells as well as on the non-cancerous human fibroblast HU2 cells" with "against human malignant melanoma A375 cells and non-cancerous fibroblast HU2 cells "

Correction has been made in the revised manuscript.

- In the Abstract, the authors claimed that they combined four agents to seek possible side effects of the drugs. How is that possible?

The aim of this study was to investigate the synergistic effects of the studied drugs in order to reduce the dose used and thus reduce their side effects. So that with increasing the number of drugs, the dose of each of them decreases.

- In the Introduction, the first sentence is too lengthy! Try to use shorter sentences throughout the manuscript.

Correction has been made in the revised manuscript.

- In Methods, the authors should mention the concentration of penicillin and streptomycin contained in the DMEM culture medium.

Correction has been made in the revised manuscript.

- Why did the authors choose these cell lines? Kindly explain in the Introduction.

Correction has been made in the revised manuscript.

- In all treatment groups, the studied anti-cancer agents have shown greater cell-killing effects on A375 cells than normal human cells. How do you explain these findings? Kindly discuss it.

Cancer cells tend to form new cells more quickly than normal cells and this makes them a better target for chemotherapy drugs. However, chemo drugs can't tell the difference between healthy cells and cancer cells. This means normal cells are damaged along with the cancer cells, and this causes side effects. Each time chemo is given, it means trying to find a balance between killing the cancer cells (in order to cure or control the disease) and sparing the normal cells (to lessen side effects).

- On what basis did the authors choose the range of escalating concentrations (7.5 to 240µg/mL)?

For this purpose, it started from a small amount and continued up to ten times the initial concentration, so that the concentrations were doubled in order.

- The authors should provide the limitations of their study at the end of the discussion.
- Combination of two or more agents must be performed based on the Chou-Talalay method. Random combining of agents will not indicate the interaction between drugs, and therefore, yields no reliable conclusion. The Chou-Talalay method for drug combination is based on the median-effect equation, derived from the mass-action law principle, which is the unified theory that provides the common link between single entity and multiple entities, and first-order and higher-order dynamics. In this equation, the combination index (CI) defines Synergism (CI < 1),

Additive Effect (CI = 1), and Antagonism (CI > 1). In this respect, the authors need to clarify why they did not use the Chou-Talalay method and consider it as a limitation to their study.

Correction has been made in the revised manuscript.

2 Revision 1

2 comments · 28 Apr 2021 – 5 May 2021

Referee 1 Reviewer

REJECT 28 Apr 2021

The article has been poorly revised. The grammar of the manuscript has not improved, and my concerns were not addressed entirely. Limitations of the study were not mentioned, and reanalyzing the combination of agents using the Chou-Talalay method affected the previous findings of the study. Collectively, the quality of the manuscript was not improved.

Editor-in-Chief

MAJOR REVISION 5 May 2021

Based on the reviewers' comments and my reading, this manuscript needs major revisions, and the authors need to reply to the comments point by point.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

We would like to thank the reviewers for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. Correction has been made in the revised manuscript as follows.

Reviewer 1:
Q: *The article is poorly revised. The manuscript is not grammatically improved and my concerns were not addressed entirely.*

Response: The article was revised and Correction of grammatical errors and English improvement were carried done. Changes in the text are highlighted in green.

Q: *Limitations of the study were not mentioned,*

Response: Study limitations were added to the article as follows

Only the MTT assay used for examining the viability of the studied cells. To overcome this limitation, it is suggested to use Flow cytometry test in order to have better understanding of the mechanism of drugs action on apoptosis or necrosis of studied cells.

Q: *re-analyzing the combination of agents using the Chou-Talalay method affected the previous findings of the study.*

Response: No synergistic reaction was recorded among different combination of drugs based on calculate CI values and that was in line with our results because our results also showed that the most significant effect on A375 cells was associated with Vincristine and Taxol+ Vincristine treatments, respectively. As showed in figure 4 no significant difference was observed between Taxol, Vincristine and Taxol + Vincristin treatments. The conclusion of article were corrected as follows

Results indicated that the most significant effects on A375 cells were associated with Vincristine treatment and no synergistic reaction was recorded among different combination of drugs based on calculate CI values by calcysyn software.

Associate Editor 1:

Q: *The authors did not revise the manuscript completely.*

Response: The article completely revised and correction has been made in the revised manuscript.

Q: *The manuscript is not grammatically improved.*

Response: Correction of grammatical errors and English improvement were carried done.

Q: *It is not suitable for publication in this format*

Response: Correction has been made in the revised manuscript.

3 Revision 2

3 comments · 17 May 2021 – 19 May 2021

Referee 1 Reviewer

ACCEPT 17 May 2021

The manuscript is improved grammatically.

Associate Editor

ACCEPT 18 May 2021

Dear editor
The manuscript has been revised completely.
Best regards

Editor-in-Chief

ACCEPT 19 May 2021

Based on the reviewer's and AE's comments, the manuscript was revised well. Thus, this manuscript can be accepted for publication in GCT.