Reviewer's report

Title: A novel copper complex induces ROS generation in doxorubicin resistant Ehrlich ascitis carcinoma cells and increases activity of antioxidant enzymes in vital organs.

Version: 1 Date: 1 September 2006

Reviewer: Nada Orsolic

Reviewer's report:

General
Multidrug resistance (MDR) is defined as the cross-resistance to a variety of agents with distinct chemical structures or mechanisms of action and is believed to be the primary obstacle to successful cancer chemotherapy. Overexpression of a family of the so-called ABC (ATP binding cassette) transporters, such as P-glycoprotein and MRP1, in the plasma membrane, which actively extrude cytotoxic agents out of the cancer cells and thus prevent efficient cell killing, is a well-recognized mechanism underlying MDR. Therefore, pharmacological inhibition of these transporters with transporter inhibitors represents a promising approach for MDR reversal. Identifying and characterizing new drugs, such as copper N-(2-hydroxyacetophenone) glycinate (CuNG) troxacitabine, their structure and mechanism of action that modulates resistance to anticancer drugs activities remains an important theme in the literature of cancer research.

This is an interesting manuscript and it acceptable for publication in BMC Cancer. The manuscript is covering the area of anticancer drug sciences. The subject fall within the scope of the journal. The work is new and original and title clearing reflect the contents. Abstract is also sufficiently informative if read in isolation. Experimental design is suitable and methods are appropriate and well described.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

a) It is not clear which vehicle was used in preparation of CuNG and was it the same for the controls.
b) More data should be needed to clarify the positive effect of the CuNG on normal and tumor cells. Discussion section is informative, clear adequately supported by data but in my opinion author should better explain differences between normal and tumor cells. Additional new information about possible mechanism(s) of antitumor activity in resistant cells by CuNG would be necessary to add for the consideration of this manuscript for publication.
c) The question of the possible effects of the CuNG on the metabolic disposition of the chemotherapeutic agents (doxorubicin) is an important one that is not mentioned in the text.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes

Declaration of competing interests:
The manuscript entitled “A novel copper complex induces ROS generation in doxorubicin resistant Ehrlich ascitis carcinoma cells and increases activity of antioxidant enzymes in vital organs” described the effect of GSH-depleting agent, a novel copper complex viz., copper N-(2hydroxyacetophenone) glycinate (CuNG), which was initially found to be a potential resistance modifying agent and later found to be an immunomodulator in mice model in different doses. The effect of CuNG has been studied on ROS generation, multidrug resistance-associated protein1 (MRP1) expression and on activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). Authors reported that in vivo treatment of novel metal chelate (CuNG) in one hand induced ROS and down-regulated surface multidrug resistance-associated protein 1 (MRP1) expression in EAC/Dox cells, and on the other hand increased activities of antioxidative enzymes in vital organs like heart, lung and kidney which might be involved in CuNG mediated decrease in ROS levels in those organs. Moreover, CuNG got excreted through urine and bile, thus rendering animals safe from copper toxicity. According to this CuNG may be a promising candidate to sensitize drug resistant cancers in the clinic.

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a) It is not clear which vehicle was used in preparation of CuNG and was it the same for the controls.

b) More data should be needed to clarify the positive effect of the CuNG on normal and tumor cells. Discussion section is informative, clear adequately supported by data but in my opinion author should better explain differs between normal and tumor cells. Additional new information about possible mechanism(s) of antitumor activity in resistant cells by CuNG would be necessary to add for the consideration of this manuscript for publication.

c) The question of the possible effects of the CuNG on the metabolic disposition of the chemotherapeutic agents (doxorubicin) is an important one that is not mentioned in the text.

To summarize, the rationale of the work is clear. Altogether, the topic of this manuscript is appropriate to the scope of the BMC Cancer. All in all, this manuscript should have minor revision to be reconsidered for publication in the BMC Cancer.