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Charles University in Prague
Faculty of Pharmacy in Hradec Králové

Hradec Králové, March 1, 2007

OPINION ON DOCTORAL THESIS

Author – postgraduate student: **Mgr. Helena Kaiserová**
Title: **Preventing anthracycline cardiotoxicity: from iron chelation to carbonyl reductase inhibition**
Supervisor: **Prof. RNDr. Eva Kvasničková, CSc.**
Workplace: **Charles University in Prague, Faculty of Pharmacy in Hradec Králové, Department of Biochemical Sciences**
Co-operating workplace: **University of Maastricht, Faculty of Medicine, Department of Pharmacology and Toxicology, Netherlands**

General characteristics

The author of this opinion suppose that it is not necessary to repeat the content of thesis, thus the opinion is focused on analysis of the virtues and possible shortcomings of the thesis.

The submitted thesis represents a set of four papers, three have been already published and one is being submitted for publication. In all papers except one is Mgr. H. Kaiserová the first author. The papers were published in journal with impact factor. The articles are provided by

Introduction, Aims of thesis, References, at the end with Conclusions, Summary and List of Publications. The thesis is written on 137 pages.

In the formal aspect the thesis is written clearly with excellent English scientific style. The reviewer found only rare minor mistakes, e.g., p. 3 (Contents), section IV: abbreviation of journal title is not correct, instead Chem should be Ch.; p. 7, Fig. 2: for clarity the structure of anthracyclines should be completed by letters (rings) or numerals (carbon atoms); p. 26, Fig. 4: the chemical name of analogue o-108 is *pyridoxal* 2-chlorobenzoyl hydrazone.

The topic

The topic of the thesis is very important as it deals with some important aspects of athracycline toxicity, namely cardiotoxicity. Chronic form of this toxicity, unfortunately, limits the usefulnes of this group of very efficient cytotoxic antibiotics. A huge effort has been devoted to find out precise pathogenesis of the anthracycline cardiotoxicity, which would enable to discover effective cardioprotectants. Dexrazoxane with iron chelating properties is the only approved protectant, however, with some disadvantegous features, e.g., necessity of parenteral administration, some degree of myelotoxicity in higher dosage. Therefore, further investivation of newer iron chelators and/or antioxidants with more favourable properties and with knowledge of their biotransformation pathways is warrant.

The results with pointing out new information

Chapter II

Kaiserova H, et al. Iron is not involved in oxidative stress-mediated cytotoxicity of doxorubicin and bleomycin. Br Med J 2006;149:920-930

In vitro study it was demonstrated that iron chelation is not the only factor in protection against doxorubicin and bleomycin cytotoxicity, which was demonstrated by dexrazoxane and monohydroxyethylrutoside.

Chapter III

Schröterová L, Kaiserová H, et al. The effect of new lipophilic chelators on activities of cytosolic reductases and P450 cytochromes involved in the metabolism of anthracycline antibiotics. Studies in vitro. Physiol Res 2004;53:683-91

New iron chelators of aroylhydrazone group – pyridoxal isonicotinoyl hydrazone (PIH) and salicylaldehyde isonicotinoyl hydrazone (SIH) – themselves having no effect on the

activities of the studied enzymes (some reductases and P450 isoenzymes) partially preserved these activities significantly reduced by doxorubicin and daunorubicin.

Chapter IV

Kaiserová H, Kvasničková E. Inhibition study of rabbit liver cytosolic reductases involved in daunorubicin toxication.

It was demonstrated that carbonyl reductase is principal reductase of daunorubicin. This fact is of importance in investigation of new protectors against anthracycline toxicity because their hydroxy metabolites are even more toxic than parent compounds.

Chapter V

Kaiserová H, et al. Flavonoids as protectants against doxorubicin cardiotoxicity: role of iron chelation, antioxidant activity and inhibition of carbonyl reductase (submitted).

Of the flavonoids studied in respect to their iron-chelating, antioxidant and carbonyl reductase-inhibitory activity only new synthetized quertenary ammonium analogues had cardioprotective effect against doxorubicin cardiotoxicity comparable with a reference drug – monohydroxyethylrutoside.

I would like to ask one question: If there was no correlation found between cardioprotective action of the mentioned subgroup of flavonoids and their iron-chelating, antioxidant and carbonyl reductase inhibiton, what are the potential underlying mechanisms of this protective action?

Conclusion

The objective of the thesis listed in part 6. (Outline and scope of the thesis, p. 30-1) have been entirely met, hence I strongly recommend the submitted work for defence.

Hdrina

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reviewer: Radomír Hrdina, Associate Prof., M.D., Ph.D.

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