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REVIEW ON DOCTORAL DISSERTATION THESIS

Author: Yu Zhang M.Sc.

Title: Study of pharmacokinetic and pharmacodynamic mechanisms of drug resistance and their modulation in non-small cell lung cancer.

Field: Pharmacology

Reviewer: prof. MUDr. Miloš Pešek, CSc.

The work is devoted to a very actual issue, it focuses on early detection of bronchogenic carcinoma. This disease is currently diagnosed mostly in advanced stages, when radical treatment options are almost out of question. This makes it all the more necessary to look for ways to improve the efficacy of systemic anticancer treatment, its tolerance, and especially how to prevent or delay the development of resistance of cancer cells to chemotherapy, targeted therapy and possibly immuno-oncological treatment.

The dissertation thesis is based on the results of seven original published papers and one paper under peer-review. The cumulative IF of the papers is 40.629, three papers were published in quartile 1 journals and four papers in quartile 2. The author's participation on each publication ranges from 10-50%.

The present work consists of six parts and has five thematic units. In the introductory chapters, the author discusses the epidemiology of non-small cell lung cancer and current modalities of systemic anticancer therapy, with a focus on chemotherapy and targeted therapy for tumors driven by targetable mutations. These therapeutic modalities are widely used, but the main problems associated with their use are adverse effects and, above all, the emergence of resistance to specific agents. Resistance mechanisms are divided into so-called target-dependent and target-independent. The author systematically discusses the mechanisms of the latter group. He focuses on the pharmacokinetic mechanisms of drug resistance and the possibilities of influencing them. He also discusses the pharmacodynamic mechanisms of drug resistance and their relevance for the development of multidrug resistance in cancer cells and analyzes in detail the signaling pathways involved in these processes. Of importance are ABC transporters, whose activity can induce resistance to anticancer drugs through active secretion of the anticancer drug substrates from cancer cells.

Another mechanism of multidrug resistance that has been investigated is drugs' metabolic inactivation by cytochrome CYP 3A4. Inhibition of this system may prevent the emergence of docetaxel resistance, according to the authors' findings, and it has been shown that drugs such as ensartinib, which act simultaneously on both transporters and metabolizing enzyme systems, can eliminate drug resistance that has already developed.

Of fundamental importance for the emergence of drug resistance are cancer stem cells, which are more resistant to anticancer therapy than daughter cells and possess many properties that allow the emergence of tumour cell populations equipped with resistance mechanisms to drugs already used or structurally and functionally similar.

The efficacy of a number of biologically targeted agents already used in clinical oncology or undergoing clinical trials has been investigated in ex vivo systems with the intention of delaying or preventing the emergence of resistant tumour cells or eliminating drug resistance that has already developed.

A serious fact in the field of targeted therapy of EGFR-driven lung cancer is the emergence of resistant cancer cell clones, which are the basis of disease relapse. The authors prepared EGFR-resistant tumor cells in 2D and 3D cell cultures and demonstrated resistance of these lines to all three EGFR inhibitors tested. Using global proteomic analysis, they demonstrated differences between the proteomes of EGFR-sensitive and EGFR-resistant tumor cells. The actual goal of the dissertation is to search for synergistic anti-cancer drugs for systemic treatment of non-small cell lung cancer, while affecting some signaling pathways such as ECM signaling or Hedgehog, may also be a contribution to the treatment of tumors of other primary localizations. The authors plan to test the findings in in vivo models.

Conclusion:

The doctoral dissertation thesis has an extensive and up-to-date literature background, and the sources cited are adequate and appropriate. Collection of publications, on which the thesis is based and of which Mr. Zhang is a significant co-author, has a high citation rate, with a total of 222 citations.

The results, measurements and observations obtained are of high quality.

The statistical treatment of the results and their graphical and tabular presentation are of a high scientific and presentational standard.

The discussion and conclusions of the presented work are entirely adequate to the current state of knowledge of the studied issue.

The work brings new significant scientific knowledge in the field of studying the possibilities of prevention and influence of drug resistance in the treatment of non-small cell lung cancer.

Therefore, I recommend Pharmacology and Toxicology Board to accept the thesis in the actual form and, on its basis, I recommend conferring the doctor (Ph.D.) title to Mr. Yu Zhang.

In Pilsen, 7 June 2023

Prof. MUDr. Miloš Pešek, CSc.