Abstract

Cancer remains one of the most pressing issues of contemporary science and medicine. Incidence of malignant diseases is rising worldwide and they represent a major problem for the society due to both economic and ethical issues they cause. Although the progress in cancer biology, therapy and immunology has led to the introduction of many novel therapeutic protocols, approaches and drugs with specificity defined on a molecular level into clinical practice, many malignancies retain their poor prognosis. Therefore, intense research into new ways to increase our therapeutic options is warranted.

Unfortunately, bringing a completely novel drug into clinical use takes extremely high amounts of time and money and entails a high risk of failure. Therefore, a promising approach has been recently adopted which lies in repurposing compounds already used in human medicine for cancer treatment. This form of research can advance through clinical trials for a new indication much easier, faster and cheaper than researching completely new drugs.

The aim of this study was to examine the anticancer potential of one such drug, mebendazole. An anthelminthic from the family of benzimidazoles, mebendazole has been in common clinical use from the 1970s and is marked by its low toxicity as well as its very low solubility. Due to this low solubility, mebendazole is only administered perorally and this application is marked by a low biological availability.

We tested the cytostatic effect of mebendazole and two of its derivatives in the model of several murine cancer cell lines with the aim of preparing HPMA copolymer-bound conjugate of mebendazole which would increase its solubility and enable parenteral application. Mebendazole and both derivatives were shown to possess cytostatic activity *in vitro* comparable to the cytostatic activity of doxorubicin.

We synthesized the HPMA copolymer-bound conjugate and tested its *in vivo* toxicity and therapeutic efficacy in the model of induced syngeneic tumors in mice. A pronounced increase in toxicity was observed and a suppression of erythropoiesis was described. Bone marrow suppression as well as acute liver toxicity were seen in histology, findings consistent with the rare reports of mebendazole toxicity from literature. The therapeutic experiments were unsuccessful due to this high toxicity; nevertheless, the experiments marked the first account of parenteral application of high molecular weight conjugate of mebendazole in mice.

Keywords: **Cancer, mebendazole, HPMA copolymer-bound drugs, drug repurposing, toxicity, mice, chemotherapy.**