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The possible mechanism of the antioxidants on the antitumor effect of bortezomib in melanoma and myeloma cell lines

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Bortezomib is a proteasome inhibitor chemotherapeutic agent used to treat multiple myeloma; recently studies offer it as a promising drug to treat melanoma. Bortezomib-induced peripheral neuropathy (BIPN) is a dose-limiting side-effect, that can be treated with antioxidants, e.g. alpha-lipoic acid and thiamine.
The objective of our experiments was: (i) to verify the cytotoxicity of bortezomib; (ii) to test and compare the influence of the antioxidants on the antitumor effect of bortezomib in melanoma and myeloma.
The cells were U266 myeloma, WM35 primary and A2058 metastatic melanoma. The concentrations were: (i) bortezomib: 20, 100 and 300 ng/mL; (ii) alpha-lipoic acid: 10 and 100 µg/mL (iii) thiamine: 150 and 300 nM. Impedimetry (xCELLigence SP) was used to evaluate the cytotoxicity. To study the cell cycle profile, Cell-Clock™, a redox dye was applied and evaluated by ImageJ. Apoptosis was analyzed by flow cytometry after annexinV assay and phospho-p53 immunostaining.
Bortezomib was cytotoxic and blocked U266 cells in the G1 phase. Alpha-lipoic acid enhanced the cytotoxicity of bortezomib (20 ng/ml) in U266 cells, but it counteracted bortezomib in melanoma cells. Thiamine (300 nM) with bortezomib antagonized the antitumor effect of bortezomib on myeloma cells. In every cell, bortezomib was apoptotic, which effect was decreased in melanoma by the co-treatments.
A good correlation between the apoptotic and the cell cycle arresting effect of bortezomib as well as the antagonistic effect of the antioxidants was found. In conclusion, the combination therapy of bortezomib and a low dose of antioxidants could be offered for the treatment of BIPN in multiple myeloma.

Biography

Angéla Takács received the Doctor of Pharmacy degree from the Semmelweis University in 2017. Currently, she is a PhD student in the Modern Trends in Pharmaceutical Scientific Research Program at the Department of Genetics Cell- and Immunobiology, Semmelweis University. Currently, she is woking on projects in connection with targeted tumor therapy.

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