Improving the efficacy of proteasome inhibitors in the treatment of renal cell carcinoma by combination with the human immunodeficiency virus (HIV)-protease inhibitors lopinavir or nelfinavir

Dominik Abt, Andrej Besse, Lenka Sedlarikova, Marianne Kraus, Juergen Bader, Tobias Silzle, Martina Vodinska, Ondrej Slaby, Hans-Peter Schmid, Daniel Stephan Engeler, Christoph Driessen & Lenka Besse

OBJECTIVES
To assess the potential of second-generation proteasome inhibition by carfilzomib and its combination with the human immunodeficiency virus (HIV) protease inhibitors (HIV-PIs) lopinavir and nelfinavir in vitro for improved treatment of clear cell renal cell cancer (ccRCC).

MATERIALS AND METHODS
Cytotoxicity, reactive oxygen species (ROS) production, and unfolded protein response (UPR) activation of proteasome inhibitors, HIV-PIs, and their combination were assessed in three cell lines and primary cells derived from three ccRCC tumours by MTS assay, flow cytometry, quantitative reverse transcriptase-polymerase chain reaction and western blot, respectively. Proteasome activity was determined by activity based probes. Flow cytometry was used to assess apoptosis by annexin V/propidium iodide assay and ATP-binding cassette sub-family B member 1 (ABCB1) activity by MitoTracker™ Green FM efflux assay (Thermo Fisher Scientific, MA, USA).

RESULTS
Lopinavir and nelfinavir significantly increased the cytotoxic effect of carfilzomib in all cell lines and primary cells. ABCB1 efflux pump inhibition, induction of ROS production, and UPR pre-activation by lopinavir were identified as underlying mechanisms of this strong synergistic effect. Combined treatment led to unresolved protein stress, increased activation of pro-apoptotic UPR pathway, and a significant increase in apoptosis.

CONCLUSION
The combination of the proteasome inhibitor carfilzomib and the HIV-PIs lopinavir and nelfinavir has a strong synergistic cytotoxic activity against ccRCCin vitro at therapeutically relevant drug concentrations. This effect is
most likely explained by synergistic UPR triggering and ABCB1-modulation caused by HIV-PIs. Our findings suggest that combined treatment of second-generation proteasome inhibitors and HIV-PIs should be investigated in patients with metastatic RCC within a clinical trial.

type: journal paper/review (English)
date of publishing: 21-11-2017
journal title: BJU Int
ISSN electronic: 1464-410X