Imatinib therapy of chronic myeloid leukemia significantly reduced carnitine intake resulting in adverse event - impaired muscle cell metabolism

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Background: A prominent, safe and efficient therapy for patients with chronic myeloid leukemia (CML) is inhibiting oncogenic protein BCR::ABL1 in a targeted manner with imatinib, a tyrosine kinase inhibitor. A substantial part of patients treated with imatinib report skeletomuscular adverse events affecting their quality of life. OCTN2 membrane transporter is involved in imatinib transportation into the cells. At the same time, the crucial physiological role of OCTN2 is cellular uptake of carnitine which is an essential co-factor for the mitochondrial β-oxidation pathway. This work investigates the impact of imatinib treatment on carnitine intake and energy metabolism of muscle cells.

Methods: HTB-153 (human rhabdomyosarcoma) cell line and KCL-22 (CML cell line) were used to study the impact of imatinib treatment on intracellular levels of carnitine and vice versa. The energy metabolism changes in cells treated by imatinib were quantified and compared to changes in cells exposed to highly specific OCTN2 inhibitor vinorelbine. Mouse models were used to test whether *in vitro* observations are also achieved *in vivo* in thigh muscle tissue. The analytes of interest were quantified using a Prominence HPLC system coupled with a tandem mass spectrometer.

Results: This work showed that through the carnitine-specific transporter OCTN2, imatinib and carnitine intake competed unequally and intracellular carnitine concentrations were significantly reduced. In contrast, carnitine preincubation did not influence imatinib cell intake or interfere with leukemia cell targeting. Blocking the intracellular supply of carnitine with imatinib significantly reduced the production of most Krebs cycle metabolites and ATP. However, subsequent carnitine supplementation rescued mitochondrial energy production. Due to specific inhibition of OCTN2 activity, the influx of carnitine was blocked and mitochondrial energy metabolism was impaired in muscle cells *in vitro* and in thigh muscle tissue in a mouse model.

Conclusions: This preclinical experimental study revealed detrimental effect of imatinib on carnitine-mediated energy metabolism of muscle cells providing a possible molecular background of the frequently occurred side effects during imatinib therapy such as fatigue, muscle pain and cramps.