PROTEIN KINASE INHIBITORS AS MODULATORS OF PHARMACOKINETIC MECHANISMS OF MULTIDRUG RESISTANCE: FOCUS ON ACUTE LEUKEMIA

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ATP-binding cassette (ABC) membrane efflux transporters are recognized as key players affecting pharmacokinetic behaviour of drugs and also rendering cancer cells resistant to conventional cytotoxic compounds. While the role of ABC transporters in multidrug resistant solid tumors remain questionable, increased expression and activity of *ABCB1* and *ABCG2* in hematological malignancies, mainly in acute myeloid and lymphoblastic leukemia, was shown to correlate with low treatment response and worse prognosis.
Inhibitors of protein kinases, in particular cyclin-dependent kinase inhibitors (CDKI) represent novel group of drugs that are able to more or less specifically target the cancer cells diminishing their proliferation and inducing apoptosis. Here, we introduce so far not described feature of several CDKI, currently undergoing clinical trials for acute leukemia treatment, as inhibitors of ABC transporters able to restore sensitivity of resistant cancer cells. Moreover, some of the compounds revealed also ability to inhibit carbonyl reducing enzymes (CREs), another pharmacokinetic mechanism leading to resistance of leukemia cells to traditional daunorubin-based therapy. Employing *in vitro* and *ex vivo* accumulation, apoptosis and ddPCR experimental approaches, we show that some of CDKI can enhance accumulation of mitoxantrone and daunorubicin in cancer cells, potentiating thereby their effect and inducing apoptotic behaviour. The linear regression calculation clearly shows that the effect relates well to the level of *ABCB1* transcripts in leukemic mononuclear cells isolated from *de novo* diagnosed AML patients. The enhanced accumulation of mitoxantrone and daunorubicin and subsequent enhancement of apoptotic population was particularly pronounced in leukemic cells of CD34+ phenotype and was also shown to correlate with FLT3 mutation status.
Thereby, we suggest that CDKI might provide double therapeutic benefit – not only (i) showing their direct action in cancer cells, but also (ii) potentiating the effect of conventional drugs administered in combination, allowing further reduction of their doses, which would be of great benefit namely for older and polymorbic patients. With right stratification of acute leukemia patients based on their phenotype and mutational status, CDKI might therefore represent new therapeutic tool improving the treatment outcomes. Nevertheless, further studies are needed to confirm this hypothesis in clinical settings.