The anti-invasive activity of synthetic alkaloid ethoxyfagaronine on L1210 leukemia cells is mediated by down-regulation of plasminogen activators and MT1-MMP expression and activity

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Résumé en anglais	Quaternary benzo[c]phenanthridines such as fagaronine are natural substances which have been reported to exhibit anticancer and anti-leukemic properties. However, the therapeutic use of these molecules is limited due to the high dose required to exhibit anti-tumor activity and subsequent toxicity. In this study, we describe the therapeutic potential of a new derivative of fagaronine, Ethoxyfagaronine (N-methyl-12-ethoxy-2hydroxy-3, 8, 9-trimethoxybenzo[c]-phenanthridiniumchlorhydrate) as an anti-leukemic agent. Cytotoxic activity and cell growth inhibition of Ethoxyfagaronine (Etxfag) was tested on murine L1210 leukemia cells using trypan blue assay and MTT assay. At the concentration of 10−7 M, Etxfag induced less than 10% of cell death. Etxfag (10−7 M) was tested on L1210 cell invasiveness using matrigel™ precoated transwell chambers and efficiently reduces the invasive potential of L1210 cells by more than 50% as compared with untreated cells. Western blot and immunofluorescence experiments showed that Etxfag decreased both MT1-MMP expression and activation at the cell surface, decreased plasmin activity by down-regulating u-PAR and uPA expression at the cell surface and increasing PAI-1 secretion in conditioned media. The set of our findings underscore the therapeutic potential of ethoxyfagaronine as a new potential anticancer agent able to prevent leukemic cell dissemination.
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