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Hepatic stellate cell-targeted imatinib nanomedicine versus conventional imatinib: A novel strategy with potent efficacy in experimental liver fibrosis

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Abstract:

Liver fibrosis is a global health problem without approved treatment. Imatinib inhibits two key profibrotic pathways; platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) and thus can be used to treat liver fibrosis. However, conventional imatinib therapy is hampered by low concentration at target tissue and increased toxicity to other tissues especially heart, lung and liver. Since hepatic stellate cells (HSCs) are the main contributors to liver fibrosis pathogenesis and sole hepatic vitamin A (V_A) storage cells, they can be actively targeted by coupling liposomes to V_A. In this study, novel V_A-coupled imatinib-loaded liposomes (ILC) were prepared and optimized regarding V_A-coupling efficiency, imatinib entrapment efficiency, and particle size. Preferential accumulation of the selected formula in liver was proved by tracing intraperitoneally (i.p.)-injected V_A-coupled liposomes loaded with Nile Red (LCNR) to rats with CCl_4-induced liver fibrosis using live animal imaging. Co-localization of LCNR with immunofluorescently-labeled PDGFR-β in frozen liver tissue sections confirmed HSCs targeting. ILC bio-distribution, following single i.p. injection, revealed 13.5 folds higher hepatic accumulation than conventional imatinib in addition to limited bio-distribution to other organs including heart and lung reflecting diminished adverse effects. ILC therapy resulted in a potent inhibition of phosphorylated PDGFR-β expression when compared to conventional imatinib. Subsequently, there was a statistically significant improvement in liver function tests and reversal of hepatotoxicity along with liver fibrosis. Anti-fibrotic effect was evident from histopathologic Ishak score reduction as well as normalization of the level of profibrotic mediators (hydroxyproline, TGF-B and matrix metalloproteinase-2). Thus, HSC-targeted imatinib therapy shows outstanding anti-fibrotic effects with reduced cytotoxicity

compared to conventional imatinib. It can represent a promising novel approach for liver fibrosis treatment. © 2017 Elsevier B.V.

Reference:

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