Ligand-directed Macromolecular Urocanic Acid Conjugate for Treating Cancer: Design and Synthesis

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The initial studies evaluating the anticancer activity of urocanic acid were performed in the 1980s. Though, if administered as a free agent, urocanic acid is known to be rapidly degraded in the human body, which results in a short circulation time and poor antitumor efficacy. To overcome this limitation, a novel prodrug has been developed, i.e. the covalent conjugate of urocanic acid with polyethyleneimine. We assumed that this conjugate would have significantly greater therapeutic index due to the protection of urocanic acid from renal clearance, which could prolong its circulation half-life. In addition, the conjugation of the prodrug with biotin will enhance the permeation and retention effect of the macromolecular drug, which will allow for the preferential accumulation of the prodrug in tumor tissues. This study was focused on the synthesis on ligand-directed anticancer macromolecular urocanic acid conjugate. The macromolecular conjugate was synthesized by the direct attachment of N-hydroxysuccinimide ester of chemotherapeutic urocanic acid to biotin-modified branched polyethyleneimine. Biotin residues were grafted onto 25 kDa polyethyleneimine by treating the polymer with N-hydroxysuccinimide activated ester of biotin. The conjugation of the biotin and urocanic acid to polyethyleneimine was confirmed by NMR and UV-vis spectroscopy. Thus, the novel conjugate prepared in this study can be a promising prodrug of urocanic acid for the future clinical use.